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SPERMATOGENESIS IN A "PAN-HYPOPITUITARY" EUNUCHOID, AS THE RESULT OF TESTOSTERONE THERAPY

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FOLLOWING the report of Walsh, Cuyler and McCullagh (2) that androgen administration resulted in stimulation of the germinal epithelium of the seminiferous tubules, numerous papers have appeared verifying and amplifying this observation. Recently Simpson and Evans (1) reported active spermatogenesis in rats hypophysectomized at 40 days of age, and then injected with testosterone propionate. To the best of our knowledge, there are no reports showing a similar train of events in humans.

We wish, at this time, to report testosterone-induced spermatogenesis in a 25 year old male showing both laboratory and clinical evidence of "panhypopituitarism," using the term in a very broad sense.

CLINICAL AND LABORATORY DATA

Patient, E. N., age 24, was first seen (through the courtesy of Dr. Herbert Evans) in August, 1946, at which time his major complaint was that of relative dwarfism and complete sexual infantilism.

His past medical history was essentially negative.

He weighed 8½ pounds at birth and grew normally until the age of 9 years. Since that time his growth had lagged far behind that of his contemporaries, although he believed that he had never completely ceased to grow.

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He had not noticed any axillary or pubic hair, enlargement of the penis or testes, or deepening of the voice. He had felt generally well and had noticed no unusual susceptibility to infection. Upper respiratory infections had not given rise to symptoms which one would expect in the case of adrenal cortical insufficiency.

Physical examination showed an immature male who could readily pass for a prepuberal boy of 12 or 13 years except for the presence of a "café-au-lait" coloration and rather deep lining and dryness of the skin such as one finds in the typical "pan-hypopituitary" individual. He weighed 96½ pounds with a height of 62½ inches and a span of

FIG. 1. Testicular biopsy before therapy (×100)

65 inches. There was slight breast enlargement which he believed had been present for some years. His voice was high; he possessed no facial, axillary or pubic hair. The external genitalia were infantile and no prostate could be palpated. His general muscular development was quite poor.

The patient had had no previous therapy except for a series of injections five years previously which he thought might have resulted in a slight increase in growth. He had no data, however, which would support this view.

Roentgen rays of the skeleton showed many open epiphyses with a bone age of 14 years or less. His 17-ketosteroid excretion was approximately 1 mg. per 24 hours and urinary gonadotropin excretion less than 3 mouse units per 24 hours.

A testicular biopsy done on September 10, 1946, showed a picture interpreted as normal prepuberal testes (Fig. 1).

It was decided to put the patient on a rather prolonged period of pregnant-mare-serum gonadotropin with the thought of getting some initial spermatogenic tubular development and then at a later date to maintain the patient on an adequate dosage of

testosterone. He accordingly was started on 20 units of "Gonadogen"[1] daily. This dose was continued for 30 days. Treatment was stopped for one week, followed by 50 units of "Gonadogen" daily for 4 weeks. It will be noted from the chart that during this medication the patient gained a small amount of weight and height (Fig. 2). There was, however, no other objective evidence of any effect of the medication. A testicular biopsy was obtained on the last day of gonadotropin therapy (Fig. 3). No significant change was noted as compared to the pretreatment biopsy. The urinary gonadotropin assay done at the end of gonadotropin therapy was negative for 4 mouse units per 24 hours and the ketosteroid excretion at this time was less than 0.5 mg. per 24 hours.

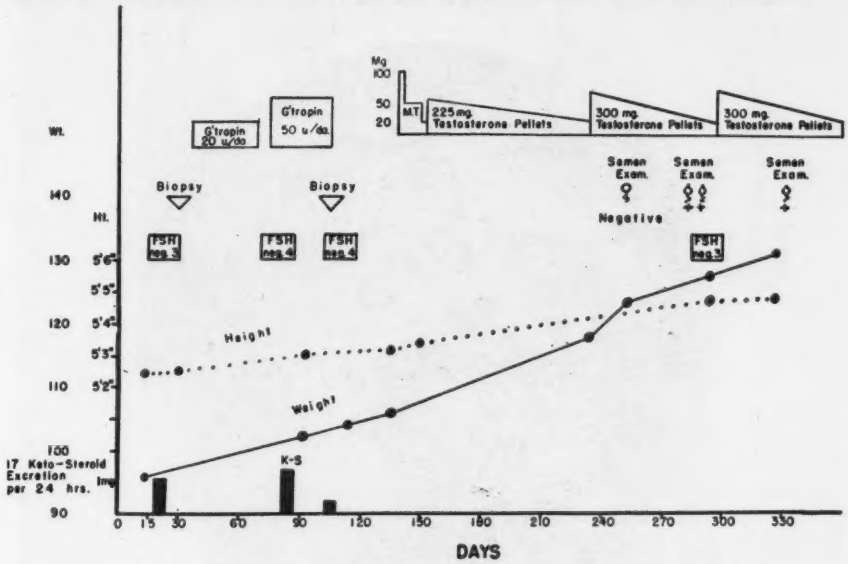

FIG. 2. Progress of patient *E. N.* over an eleven month period.

All therapy was discontinued for a period of one month, during which time he continued to gain weight at the same rate as had been the case during gonadotropin therapy. On December 17, 1946, he was placed on methyl testosterone[2] by mouth for a period of 18 days followed by testosterone pellet implantation on January 4, 1947, March 24, 1947, and on May 24, 1947 (Fig. 2).

It will be noted from the chart and from photographs after four months of testosterone therapy that he experienced a significant gain both in height and weight during his testosterone therapy (Fig. 4). The penis during this period enlarged several fold, the testes became somewhat larger and after four months of therapy his prostate was within the lower limits of normal in size.

[1] This preparation was supplied through the courtesy of the Upjohn Company. The "Units" are Cartland-Nelson Units, 1 Unit being equivalent to approximately 20 International Units.

[2] The preparations of testosterone used in this study were supplied through the courtesy of Dr. Henderson of the Schering Corporation.

He had become aware of an occasional nocturnal emission after about 3 months on testosterone. On April 12, 1947, a specimen of ejaculate was obtained and examined grossly. No mature sperm were found in the unconcentrated specimen. On May 10, 1947, an ejaculate was again examined and a count of approximately 2,000,000 mature sperm per cubic cm. was noted. The total volume of ejaculate was less than 0.5 cc. An ejaculate was again examined on May 20. At this time the count had increased to 15,000,000 per cubic cm. and the total volume to almost 1 cc. A gonadotropin assay performed on a 24 hour specimen of urine collected on May 25 was negative for 3 mouse units of gonadotropin per 24 hours.

Reexamination of ejaculate on June 27 showed 18,000,000 mature sperm per cubic

FIG. 3. Testicular biopsy after treatment for two months with pregnant mare serum ($\times$ 140)

cm. The total volume of ejaculate was 1.2 cc. A final testicular biopsy will be performed when spermatogenesis has apparently reached a maximum level, as indicated by serial sperm counts.

DISCUSSION

With the exception of the demonstration of spermatogenesis, all the results obtained in this patient have been reported by many observers on individuals with varying degrees of "pan-hypopituitarism" again using this term in a very loose and broad sense. With the demonstration of normal sperm in this individual, the immediate question was obviously whether testosterone alone had been responsible, through a direct effect

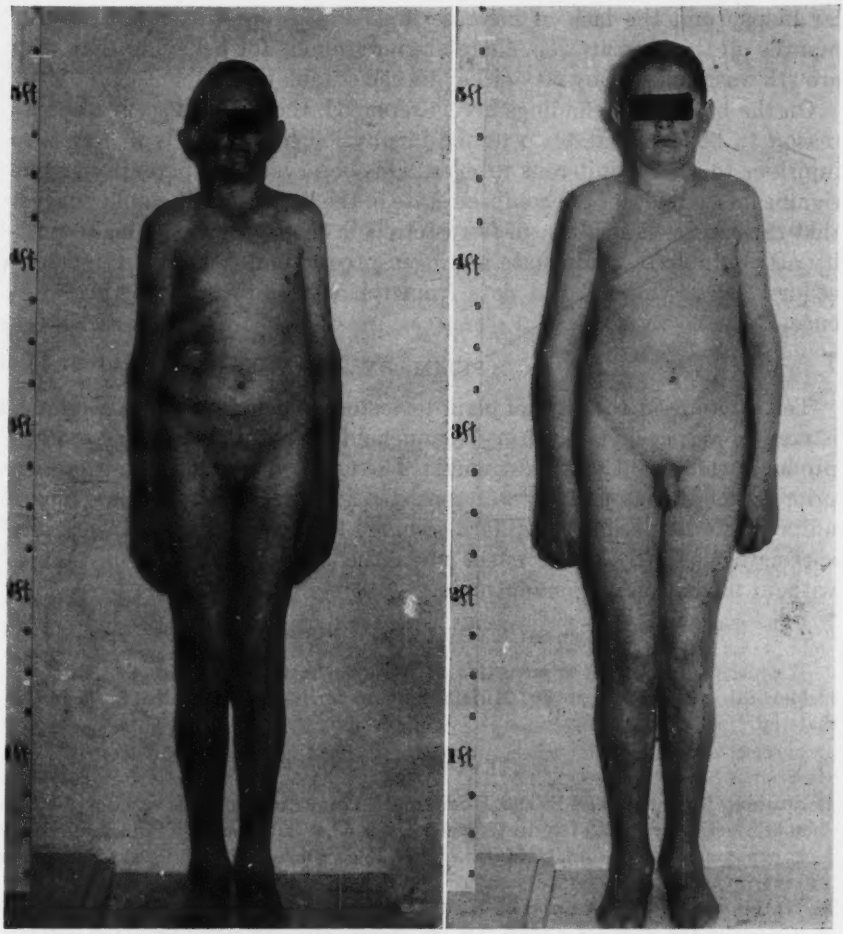

FIG. 4. Patient *E. N.*, age 24. A. Before treatment. B. After four months of testosterone therapy.

upon the seminiferous tubules or whether his own pituitary had been stimulated by testosterone to produce gonadotropin. The negative gonadotropin titer in the urine taken after the individual had been on testosterone for five months and at a time when he had a sperm count of 15,000,000 per cc. would seem to indicate beyond any reasonable doubt that testosterone produced spermatogenesis by direct effect upon the seminiferous tubules.

The slight increase in height and weight noted during the period of "Gonadogen" administration may indicate some slight growth response to this preparation. In view of the lack of significant change in the testicu-

lar biopsy and the lack of increase in 17-kestosteroid excretion after 2 months on this preparation, there are no grounds for believing that such growth was produced by way of Leydig cell stimulation.

On the basis of the findings herein reported, there would seem to be no reason to believe that testosterone in physiologic dosage is in any way injurious to the seminiferous tubules. This observation is perhaps of some significance in view of the confused state of the literature. It would suggest that the careful clinical use of testosterone in the treatment of male sterility attributable to inadequate androgen production may be a sound procedure. As yet unpublished data from this clinic substantiate this inference.

SUMMARY

Testosterone in the form of plain testosterone pellets (Schering) administered to a "pan-hypopituitary" eunuchoid over a period of five months produced significant spermatogenesis. The urinary gonadotropin excretion prior to and during therapy was consistently negative for 4 or less mouse units per 24 hours. It is therefore assumed that testosterone can produce spermatogenesis by direct effect upon the human seminiferous tubules without mediation by gonadotropin.

ACKNOWLEDGMENT

We wish to express our appreciation to Dr. John Shaver for his preparation of the histological sections, and to Dr. Miriam Simpson for her aid in evaluation of biopsy material.

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THE ENDOCRINE DISORDERS ASSOCIATED WITH CUSHING'S SYNDROME AND VIRILISM

REPORT OF AN UNUSUAL CASE

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THE nature of the pathological disturbances which are responsible for Cushing's syndrome and virilism is controversial. It therefore seems justifiable to report an unusual case in the hope that it may throw further light on this difficult question.

Case Report

An unmarried woman, age 38, was admitted to the London Hospital under the Medical Unit (Professor Arthur Ellis) on March 11, 1938. She had had a previous illness in the autumn of 1932. This commenced with amenorrhea and in the course of about three months she became grossly obese. Her mother subsequently volunteered that it was remarkable that her limbs had remained thin. Her face became dark red and she grew a moustache and beard. Broad lines appeared on her abdomen which she remembered particularly on account of their purple coloration, and she developed many bruises on her arms and legs without any apparent cause. She also had crops of "pimples" on her face, back and chest. During this illness she visited her panel doctor, Dr. Perchman, who subsequently wrote: "She was then very obese looking with marked double chin, hypertrichosis, dusky skin, but not very fat in the limbs. B.P. 140/100, no sugar in urine. She seemed to me to be a case of Cushing's pituitary-adrenal syndrome."

She refused to visit a hospital and the symptoms lasted for from two to two and a half years. Her appearance is shown in Fig. 1. Then the obesity, red color, striae and spots all disappeared and menstruation again became normal. Most of the abnormal hair on the face also disappeared, but she was left with a slight moustache. She remained well until November, 1937, when she again failed to menstruate. She had a scanty menstrual period in December and again in January, 1938, but subsequently she had complete amenorrhea. In January, 1938, she developed a sudden cough and pain in the right shoulder. Her doctor reported a tachycardia of 144 without fever. Subsequently she had all her teeth removed and a few days later she collapsed with precordial pain, dyspnea and multiple joint-pains. Her doctor found her cyanosed and she had a temperature of 103° F and a pulse rate of 140 per minute. About this time the hair began to increase on her face, but it never became as marked as in her previous illness in 1932. She remained in bed becoming progressively worse but her weight was stationary around 143 lbs. Her bowels were regular and her appetite remained good until just before admission when she developed edema of the legs and became disoriented.

On examination she was orthopnoeic with slight cyanosis of the lips and a malar flush but no abnormal pigmentation of the skin. There was abundant stiff black hair on the sides of the cheeks, upper lip, chin and axillae and the pubic hair extended up to the

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umbilicus. A little acne vulgaris was present on the cheeks, forehead and chest. There was moderate obesity of the face, neck, trunk and limbs and a small pad of fat over the lower cervical vertebrae. A few faint bluish white striae were present in the skin of the abdomen. There was gross pitting edema of the legs extending up to the lower part of the abdomen and lumbar region. The pulse was regular at 120 to 140 per minute, the heart sounds normal and blood pressure 130/80 mm. Hg. There were signs of fluid at the base of the right lung. The veins in the right lower abdominal wall were dilated but

FIG. 1.

there were no definite signs of ascites. The liver edge was palpable from 3 to 4 inches below the right costal margin and was tender. There was some resistance in the right lower quadrant but no definite palpable mass. Apart from the mental disorientation the central nervous system was normal. The hemoglobin was from 61 to 76 per cent with from 3,000,000 to 3,800,000 red blood cells per cu. mm. The white count was normal. The plasma proteins were 5.75 gm. per 100 cc. The pleural effusion contained 90 per cent lymphocytes and was sterile. She was incontinent and an estimation of 17-ketosteroid output was not made. Her mental and general condition deteriorated rapidly and she died 17 days after admission.

SUMMARY OF NECROPSY. (P.M. 140. 1938)

By Professor Dorothy Russell

Edema and collapse of the lungs. Carcinoma of suprarenal cortex.

A mass (12 × 12 × 8.5 cm.) of lobulated growth, with a thin fibrous capsule, and composed of soft opaque yellow necrotic or white and pinkish-grey tissue containing haemorrhages and a few cysts, replaced the right suprarenal body. The growth had invaded the inferior vena cava downwards for 4 cm. below the right suprarenal vein, and upwards for 10 cm. to fill the greatly dilated intra-hepatic part of the vena cava and just projected into the right auricle. There was conspicuous edema of the lower limbs and of the lumbar region. A few nodules of secondary growth were present in both lobes of the left lung and, more numerous, in the right lung. An embolus of growth was lightly adherent to bifurcation of the right pulmonary artery in the hilum of the lung. There was complete collapse of the lower lobe of the right lung and partial collapse of the lower lobe of the left lung. There was a slightly blood-stained right pleural effusion (8 oz.) and ascites (28 oz.). There were nodules of secondary growth in the liver. There was back pressure congestion and, microscopically, slight focal fatty change in the liver. There was no hypertrophy of the heart and slight general atheroma. Congestion and postmortem degeneration were present in the kidneys with, microscopically, slight focal fatty degeneration of the epithelium in the loops of Henle. There was congestion and, microscopically, slight infiltration of the pulp of the spleen with plasma cells and eosinophil leucocytes. The thymus was mainly adipose but showed, microscopically, a few cords of glandular tissue. There was abundant colloid in the normal thyroid and the four parathyroids were normal. There was great cortical atrophy in the left suprarenal body showing, microscopically, great irregularity of zonal architecture and considerable increase of fibrous stroma, and a patchy distribution of doubly refractive sudanophil lipoid and very scanty pigment. The pituitary was of normal size and macroscopic appearance and the pancreas was normal. The uterus was normal and a few follicular cysts and corpora atretica were present in the ovaries. There was scanty glandular tissue in the breasts. The brain was normal. Red marrow was present in the upper third of the shaft and in the neck of the right femur. Healed fractures were present in five ribs on the left, and six ribs on the right with osteophytic outgrowths projecting into the intercostal spaces at three sites. No recognizable osteoporosis was present in the ribs or vertebrae. The middle ears and accessory air-sinuses of the skull were normal. There was hirsuties of the face in the beard and moustache area. There was abundant hair in the axillae and, of masculine distribution, in the pubic region and less marked hirsuties of the thighs and forearms. The labia majora were prominent and the clitoris slightly enlarged, the glans measuring 1.4 cm. in length, and the corpus cavernosum 3 cm. back to the pubic arch. There was slight obesity of the trunk and lower limbs. There were narrow striae on the lower abdomen and upper part of the thighs.

Weights: Left kidney, 204.7 Gm.; left suprarenal, 2.05 Gm.; spleen 224.2 Gm.; pituitary, 0.7 Gm.; thyroid 25.2 Gm.; thymus 43.05 Gm.; pancreas, 79.6 Gm.; ovaries 8 Gm.; brain 1452 Gm.

MICROSCOPIC EXAMINATION

Right suprarenal tumor. Much of the tissue was necrotic. The surviving tumor cells collected about the blood-vessels, which were engorged, were polymorphic including spindle-forms, and mostly measured from 8 to 12 μ in diameter. Their boundaries were

ill-defined, the cytoplasm being flocculent, eosinophilic and occasionally vacuolated. Sudanophilic, isotrophic droplets were abundant in frozen sections in areas where degeneration was in progress. Unstained anisotropic lipoid was also abundant and occupied many of the better preserved cells. In sections stained for glycogen by Best's carmine method a moderate amount was present in the cytoplasm in a few restricted foci. The nuclei of the cells were relatively large and contained a heavy net of chromatin and inconspicuous nucleoli. Large uninucleate and multinucleate giant-cells were rather numerous, and in these the nuclei often contained conspicuously large eosinophilic nucleoli. The connective tissue stroma of the tumor was scanty.

A secondary deposit in the liver showed similar histological appearances.

The endocrine glands were all examined microscopically and, with the exception of the pituitary, the results of the examination have already been noted above.

The anterior lobe of the pituitary, stained with acid-fuchsin aniline-blue, was well preserved. Under low powers of the microscope, the basophilic cells appeared to be numerically reduced. A differential count was not made. With high magnifications the majority of the basophilic cells appeared to be normal mature examples. But a good many transitional basophils with fine, sky-blue granules were also present. A small minority of the cells showed the hyaline cytoplasmic change characteristic of Cushing's syndrome (4); in most instances the change was but slightly developed though in a few it was conspicuous. The other cellular constituents of the pituitary appeared normal.

DISCUSSION

The development of Cushing's syndrome and of virilism at different times in the same individual is interesting. At the height of basophilism our patient had characteristic obesity sparing the limbs, a florid dusky complexion, facial hirsuties, acne vulgaris, a tendency to bruise easily, amenorrhea, and presumably osteoporosis. The symptoms lasted for about two and a half years, and then disappeared spontaneously for two and a half years, after which the facial hirsuties and amenorrhea recurred, and she died in about four months with a metastasizing carcinoma of the right adrenal cortex.

It might be argued that the symptoms of Cushing's syndrome had recurred but were masked by the malignant growth resulting in anemia and the absence of obesity. When Cushing's syndrome occurs with a malignant adrenal cortical tumor the patient may lose weight rapidly, but in two such cases seen by the author the patients volunteered the information that their faces were fatter and they presented other unmistakable signs of Cushing's syndrome. Conversely it might be argued that the amenorrhea which was late in developing was the result of the malignant growth and the only endocrine symptom present was the hirsuties which she had had since she first developed Cushing's syndrome. Her mother confirmed that the moustache and beard practically disappeared after the Cushing's syndrome was cured and it increased with the symptoms of adrenal tumor and was marked at the time of her death. It therefore seems justifiable to claim that she had virilism at the time of her death.

The disorder of function which led to this train of events is not clear but it is well known that both Cushing's syndrome and virilism may be associated with either hyperplasia or neoplasm of the adrenal cortex. Moreover it is fair to assume that when the patient had Cushing's syndrome the basophilic cells in the anterior lobe of her pituitary gland had undergone the characteristic hyaline change described by the author (4) but, at autopsy only minimal changes were found associated with virilism. This conforms with our previous experience, and with that of Thompson and Eisenhardt (16) who examined the pituitary glands in a large series of cases of Cushing's syndrome and virilism. It may be assumed, therefore, that this change represents an alteration in the physiological activity of the basophilic cells in Cushing's syndrome which is not present in virilism. We considered that the hyaline basophilic cells appear to be healthy and not degenerating, a view shared by others on cytological grounds (12, 13, 14). Moreover similar cells occurred in the minute fragments of pituitary which remained after incomplete hypophysectomy in rats (8). These rats were still growing, albeit at a reduced rate, and their pituitary fragments must have been working hard to permit any growth to occur. We therefore concluded that hyaline cells are associated with an increased function of the pituitary gland.

Both Albright (1) and Kepler (11) have stated on theoretical grounds that the hyaline basophilic cells represent a secondary degenerative condition and that the primary disorder is in the adrenal cortex. Heinbecker (10), who also believed that the pituitary change is degenerative, claimed that it is due to a primary lesion in the hypothalamus of patients dying of Cushing's syndrome without adrenal cortical tumors. It seems certain that changes in the function of the adrenal cortex are essential in both Cushing's syndrome and in virilism but this assumption may still be in keeping with our own theory that the hyaline change is associated with an increase of pituitary function.

In order to elucidate this problem it is necessary first to consider the source of the adrenal cortical hormones. Grollman (9) suggested that the androgens are derived from cells in a special 'androgenic zone' supposed to exist in the innermost layers of the cortex adjacent to the medulla, and this theory has been widely accepted. Zwemer, Wotton and Norkus (19), however, confirming the work of earlier investigators, showed that the cortical cells developed continuously from cells just beneath the capsule and that they differentiate progressively as they pass successively through the zona glomerulosa to ripen in the zona fasciculata and to degenerate in the zona reticularis where they finally disappear in the region adjacent to the medulla. This is confirmed by our findings that after hypophysectomy the adrenal cortex atrophies progressively from within outwards and no

histological abnormality occurs in the outermost zone (8). Thus it is probable that the cortical hormones are elaborated progressively into functionally completely developed steroids and then secreted by the cortical cells as they develop from without inwards. The androgenic steroids, which have no vital function, may be formed during this development or they may be breakdown products of the completely developed steroids but we find no evidence of a special androgenic zone in man.

It seems likely that in pathological lesions of the cortex, either tumors or hyperplasia, the constituent cells are at different stages of maturity in the different clinical disorders. The androgenic tumors and hyperplasia causing virilism would be composed mainly of either unripe or degenerating cortical cells, and the tumors and hyperplasia associated with Cushing's syndrome would be composed mainly of ripe cortical cells secreting fully formed corticosterones (3). The relationship of the pituitary gland to the different clinical disorders is demonstrated by the presence of hyaline basophilic cells in Cushing's syndrome but not in virilism or in cortical tumors unassociated with any endocrine manifestations. If these hyaline cells represent increased pituitary function as we have claimed, then it is clear that the ripening of the cortical cells in pathological conditions of the adrenal cortex is dependent on the increased production of the adrenotropic hormone by the pituitary gland. The final proof of this depends upon the satisfactory demonstration of an increased production of this hormone in Cushing's syndrome compared with that in virilism.

These theories would explain several perplexing observations. They would account for the very high androgen output in patients with virilism caused by adrenal cortical tumors composed of incompletely developed cells, producing mainly androgens and the lower output in patients with Cushing's syndrome caused by adrenal cortical tumors composed of completely developed or ripe cells which produce fully formed corticosterones. Secondly they would account for the remarkable unilateral atrophy of the adrenal cortex in patients with Cushing's syndrome associated with a tumor of the other adrenal. Such tumors produce a great excess of corticosterones (17) and it has been shown that certain of these hormones cause cortical atrophy in the experimental animal. Thus a greatly increased output of such substances by the tumor would result in atrophy of the remaining healthy adrenal cortex. Conversely, in women with virilism caused by an adrenal cortical tumor, the opposite adrenal is not atrophied. This is because the incompletely elaborated steroids which are being produced in excess do not cause cortical atrophy. Thirdly they would explain the occasional incidence of Addison's disease in children with adrenal cortical hyperplasia, often associated with pseudohermaphroditism or pubertas praecox (2, 15, 18). In these patients large amounts of androgens are produced to

the exclusion of fully developed corticosterones. Here is a relatively insufficient drive from the pituitary gland leading to the production of an inadequate amount of fully developed corticosterones. Fourthly they would account for the normal or only slightly increased output of androgens in patients with Cushing's syndrome without adrenal cortical tumor. In this condition the anterior pituitary gland acting as the instigator stimulates both adrenal cortices and this results in bilateral cortical hyperplasia and the production mainly of completely elaborated corticosterones.

There remains one outstanding question. Is it possible that in Cushing's syndrome associated with an adrenal cortical tumor, the pituitary gland acting as the primary instigator has stimulated the development of the adrenal neoplasm? The only evidence bearing on this question which has so far come to our attention is the finding of four cases of Cushing's syndrome associated with carcinoma of the pancreas (6). Three of these occurred in women aged thirty years or younger, an age at which carcinoma of the pancreas is very rare. We showed statistically that the chance of one such association is 0.015, of two, 0.000225 and of three, 0.000,003,375. If, as seems evident, this association is not fortuitous it follows that in Cushing's syndrome there is a propensity to tumor formation, a suggestion already made by McLetchie (12).

To return to the patient described in this paper, it is suggested that at the time of her Cushing's syndrome the pituitary drove her adrenal cortex to hyperplasia and perhaps to benign tumor formation with the production of an excess of completely formed corticosterones: that this hyperplasia or growth became arrested with the subsidence of pituitary stimulation, but at a later date malignant changes occurred which, in the absence of a marked pituitary drive, resulted in the production of incompletely formed corticosterones and a correspondingly increased output of androsterones causing virilism.

SUMMARY

An unusual case is described of a woman who developed Cushing's syndrome with spontaneous remission. Subsequently she developed the clinical picture of virilism associated with an adrenal cortical carcinoma. Details of the necropsy are given. The endocrine disturbances responsible for Cushing's syndrome and virilism are discussed.

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A RAPID METHOD FOR THE DETERMINATION OF TOTAL URINARY 17-KETOSTEROIDS

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DURING a metabolic study it was found necessary to determine total urinary 17-ketosteroids. Since many other urine analyses had to be performed, only a small volume of urine was available for 17-ketosteroid assay. In addition, the determinations had to be done within a limited period of time and on a large scale. Since the accepted methods (3, 7, 11, 12) required a minimum volume of approximately 500 ml. and a large amount of space and equipment, it was evident that modifications would have to be made.

Hydrolysis prior to extraction was introduced independently by two different groups of workers (4, 9) after the need for acidification of urine before extraction of capon-comb-growth-producing substance had been shown (1, 5, 6). Hydrolysis can be done prior to or simultaneously with extraction with a solvent. The latter procedure requires relatively expensive apparatus, a large volume of urine, carefully regulated conditions and much time.

Because of the ease of modification, independent hydrolysis lent itself more readily to the purposes of this investigation. However, since all the previous work was done on large volumes of urine, it was felt necessary to study the conditions for the hydrolysis and extraction of 17-ketosteroids in volumes of urine of 5 to 50 ml. These studies are reported in this paper.

EXPERIMENTAL

Effect of time, temperature and concentration of acid on hydrolysis. Twenty ml. samples of normal male urine were hydrolyzed, with variations of time, temperature, and concentration of acid. Five ml. aliquots were assayed by the Holtorff-Koch modification (8) of the Zimmerman method. The results, as shown in Table 1, indicate that after heating for 10 minutes yields of 17-ketosteroids are low below 80°C. and above 100°C. Further,

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there is no advantage in using concentrations of hydrochloric acid above 30 per cent. The highest yields were obtained at 80°C. after 10 minutes or at 100°C. after 10 or 20 minutes with 30 per cent acid by volume. However, it was found that recovery of pure dehydroisoandrosterone added to urine prior to hydrolysis at 100°C. for 10 or 20 minutes varied from 82 per cent to 90 per cent; recovery of dehydroisoandrosterone after hydrolysis at 80°C. for 10 minutes varied from 94 per cent to 104 per cent. This indicated greater destruction of certain pure hormones at 100°C. than was present with hydrolysis at 80°C. It was also found that evaporation during

TABLE 1. EFFECT ON URINARY 17-KETOSTEROID YIELD* OF VARYING (a), TIME OF HEATING AND (b), ACID CONCENTRATION OF URINE SAMPLES DURING HYDROLYSIS AT 80°C.

Spec. No.	Time Minutes	Per Cent by Volume of Concentrated Hydrochloric Acid										
		0	10	20	25	30	35	40	50	60	80	100
1	10	—	—	22.7	—	26.9	24.1	—	—	—	—	—
1	20	—	—	23.8	—	25.2	23.0	—	—	—	—	—
1	60	—	—	23.0	—	23.2	13.5	—	—	—	—	—
2	10	0	4.2	27.4		29.1	—	—	27.9	26.1	29.7	27.9
3	10	—	—	—	14.6	16.0	15.5	15.2	—	—	—	—

* Yields are given as milligram equivalents of dehydroisoandrosterone per 24 hours. Each result given is the average of 8 to 12 determinations.

hydrolysis at 100°C. was significantly greater than at 80°C. Therefore 80°C. was considered the most desirable temperature for hydrolysis.

Extraction and washing. Urine plus 30 per cent by volume[1] concentrated hydrochloric acid was heated at 80°C. for 10 minutes. Five ml. aliquots of hydrolyzed urine were extracted with petroleum ether, benzol, carbon tetrachloride or ethyl ether. Results are shown in Table 2. Petroleum ether yielded results which were much lower than those obtained with the other solvents. Ethyl ether was used as the solvent in this study because it extracted as much or more than the other solvents, did not form emulsions easily, and evaporated without excessive heating. Volumes of ether less than 20 ml. formed emulsions and larger volumes did not give increased yields. Rapid and vigorous shaking for 30 seconds was found adequate to obtain the intimate contact between solvent and solute necessary for the complete removal of 17-ketosteroids.

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[1] Per cent by volume is defined as $\frac{\text{Volume HCl used to hydrolyze urine}}{\text{Volume of urine being hydrolyzed}} \times 100$.

One 10 ml. wash with 10 per cent sodium hydroxide followed by one wash with water was found sufficient to remove estrogens and other interfering substances. Additional washes with sodium hydroxide. sodium bicarbonate or water did not remove additional impurities.

TABLE 2. AMOUNT OF 17-KETOSTEROID EXTRACTED WITH DIFFERENT SOLVENTS FROM URINE HYDROLYZED AT 80°C. FOR 10 MINUTES

Results expressed as micrograms per 10 cc. sample

Spec. No.	Solvents			
	Ethyl Ether	Petroleum Ether	Carbon Tetrachloride	Benzol
1	38.0	16.0	26.5	28.2
2	25.0	15.3	25.5	25.3
3	39.7	29.7	38.0	39.7

METHOD

Based on the above experimental data the following procedure is suggested as being the most practical and accurate one for the determination of total urinary 17-ketosteroids.

Reagents. Absolute ethyl ether—reagent grade.

Absolute alcohol—commercial grade is usually suitable but it is best to run a Zimmerman test blank before using.

m-dinitrobenzene—Purify by heating in 10 per cent aqueous sodium hydroxide solution until melted. Decant while hot. Cool and wash twice with water. Add 95 per cent alcohol and dissolve by warming; keep temperatures below 50°C. Cool, add five volumes of distilled water and filter. Wash the precipitate twice with water and dry. Two per cent m-dinitrobenzene solution is made by dissolving 0.9 grams m-dinitrobenzene in 45 ml. absolute alcohol. Run a Zimmerman test blank on the reagent before using. It may be necessary to crystallize from alcohol again if blanks are high.

Potassium hydroxide—Five normal aqueous solutions of electrolytic grade KOH. Determine the normality with standard hydrochloric acid using methyl red as the indicator.

Sodium hydroxide—Solution of 10 Gm. reagent grade NaOH per 100 ml. water.

Concentrated hydrochloric acid—reagent grade. 37.5 per cent HCl. (by volume). In this paper the per cent of HCl by volume is defined as volumes of concentrated HCl per 100 volumes of urine.

It is advisable to run preliminary Zimmerman test reagent blanks to determine the purity of reagents.

Procedure. Place 10 ml. of urine and 3 ml. of concentrated HCl in a 125 ml. Erlenmeyer flask and stopper the flask with a Pyrex flathead stopper Heat the flask in a water bath at 80°C. for 10 minutes, cool and transfer 5 ml. of the hydrolysate to a 125 ml. separatory funnel. Add 20 ml. ether and shake the funnel for 30 seconds. Remove the urine. Wash the ether once with 10 ml. of 10 per cent NaOH and once with 10 ml. of distilled water; shake for 10 seconds with each wash. Remove 5 ml. of ether, evaporate the 5 ml., and assay by means of the Zimmerman reaction (8). Similar aliquots can be taken for other assay methods such as the Pincus (10).

In our determinations, the Zimmerman was performed as follows. Add 0.2 ml. absolute alcohol, 0.2 ml. of the m-dinitrobenzene solution, and 0.3 ml. of the 5N KOH solution to the dried extract. Keep the solution in the dark in a water bath whose temperature is 27° for 90 minutes. After 90 minutes dilute the solution with 1 ml. of diluent; the diluent consists of three parts of absolute alcohol to one part of water. Read the diluted solution in a colorimeter[2] using a green filter.

Prepare the standard as directed above substituting 0.20 ml. of a solution of dehydroisoandrosterone in absolute alcohol (1.0 microgram hormone per 0.01 ml. alcohol) for the 0.20 ml. absolute alcohol and omitting the ether extract.

Prepare the urine blank as above, adding 0.20 ml. absolute alcohol in place of 0.20 m-dinitrobenzene solution.

Prepare method blanks by substituting water for urine in the hydrolysis and extraction; then proceed as above.

Prepare the Zimmerman reagent blanks as above, omitting the ether extract.

RESULTS

Reproducibility. Duplicate samples of urine were assayed to determine the reproducibility of results. In over a hundred specimens the duplicates agreed within 5 per cent.

Normals. Twenty-four hour urine specimens from 35 normal young men between the ages of 20 and 30 were assayed for total urinary 17-ketosteroids. Determinations were made on 95 twenty-four hour specimens and the average 24 hour 17-ketosteroid excretion was found to be 16.9 mg. The amount excreted in 24 hours ranged from 10.0 mg. to 28.9 mg. with a mode falling between 16 and 17 mg. Seventy-nine per cent of the 24 hour speci-

[2] The Drekter-Hoskins colorimeter was used in the present experiments.

mens assayed contained between 10.0 and 20.0 mg. of the 17-ketosteroid material.

Recovery. Varying amounts of androsterone, dehydroisoandrosterone and testosterone were added to urine.[3] The urine was then hydrolyzed at 80°C. for 10 minutes. Five ml. aliquots were then extracted with 20 ml. ethyl ether, washed with NaOH and water, and a portion of the ether extract evaporated and assayed. Results indicate that androsterone, dehydroisoandrosterone and testosterone can be recovered quantitatively.

COMMENT

The proposed method is simpler than existing techniques. It has the advantage of requiring only small volumes of urine and ordinary inexpensive laboratory equipment. Furthermore, there is a considerable saving of time, which permits a complete determination to be done within three hours. Results are easily duplicated and agree well with those reported by Barnett et al. (2).

Results show that although slight increases in temperature and time of heating during hydrolysis do not affect results, it is advisable to maintain a minimum temperature of 80°C. for not less than 10 minutes. Poor recovery of dehydroisoandrosterone at 100°C. indicates the necessity for avoiding excessive heating. The amount of acid used should be 30 per cent by volume or more.

The method is flexible and can be easily adapted to the assay of volumes of urine smaller than 5 ml. or larger than 20 ml.

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[3] We are indebted to Dr. Edward Henderson of the Schering Corporation and Dr. I. S. Kleiner, Professor of Biochemistry at the New York Medical College, for generous supplies of the pure hormones used.

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SPECIFIC RENAL FUNCTIONS IN HYPERTHYROIDISM AND MYXEDEMA

EFFECTS OF TREATMENT

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THE abnormalities of metabolism and blood flow which characterize hyperthyroidism and myxedema have their effect on the kidneys. Urea clearance is depressed during myxedema although maximum specific gravity is not (2). But the kind and degree of renal functional changes in these diseases have not been analyzed by specific clearance methods. These enable the measurement of renal blood flow, glomerular filtration rate, tubular secretory capacity and, by calculation, renal vascular resistance. The purpose of this report is to describe observations before and after treatment in 4 patients, 2 suffering from hyperthyroidism and 2 from myxedema.

PROCEDURES

Brief protocols of each patient are appended to this report. One of the hyperthyroid patients was treated by subtotal thyroidectomy (Dr. Goethe Link) and the other with thiouracil. The two patients suffering from myxedema were treated by oral administration of desiccated thyroid.

Routine observations include electrocardiography, cardiac teleroentgenography and frequent determinations of basal metabolic rate. The special studies of renal function were made shortly after admission to the hospital and repeated when the effects of treatment were established. These studies consisted in determination of the renal plasma clearances of diodrast and inulin and measurement of tubular secretory capacity for diodrast (Tm_D). The procedures were substantially as described by Smith, Goldring and Chasis (9). The analytical methods were those of Corcoran and Page (4). The values reported are means of three satisfactory periods of urine collection and clearance measurement.

Plasma diodrast clearance is accepted as the equivalent of minimal renal plasma flow (RPF); the value RPF/1-hematocrit ratio is taken as the minimal rate of renal blood flow. Plasma inulin clearance measures the rate of glomerular filtration. The ratio of the clearances inulin/diodrast, known as filtration fraction (FF) expresses the proportion of water filtered

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through the glomerular capillaries from the plasma which perfuses them. Tm_D measures the maximum capacity of tubular cells to transfer diodrast from plasma to tubular fluid. This process involves the expenditure of cellular energy. In most situations, the function Tm_D can be taken as measuring the mass of functioning tissue. This can hardly be the case in diseases such as hyperthyroidism and myxedema in which tissue metabolism is seriously disturbed. Consequently, in this report, the function Tm_D is considered only as a measure of the metabolic acitivity of the tubular system concerned with the secretion of diodrast. The principles on which these interpretations are based are considered in detail elsewhere (5, 9). Renal vascular resistances were calculated by the method of Lamport (8). The R_A is taken as measuring resistance in the afferent vascular tract (aorta to end of glomerular capillaries) and R_E as measuring efferent resistance, principally that of the efferent arterioles.

OBSERVATIONS

The data are summarized in Table 1.

TABLE 1. EFFECTS ON RENAL FUNCTION OF HYPERTHYROIDISM AND MYXEDEMA. RESULTS OF TREATMENT

Patient No.	Ante (A) or Post (P) Treatment	Renal Blood *Flow* cc. per min.	Glomerular Filtration *Rate* cc. per min.	Filtration Fraction	Tubular Secretory Capacity mg. D-I. per min.	R_A	R_E	Arterial Pressure mm. Hg	Basal Metabolic Rate %
1	A	810	112	0.23	35.4	.055	.018	150/55	+83
	P	795	119	0.27	32.3	.042	.018	120/88	+14
2	A	812	74	0.14	40	.062	.010	140/75	+58
	P	615	67	0.18	35.5	.079	.015	130/90	+19
3	A	509	55	0.17	11.1	.065	.018	105/80	−31
	P	600	101	0.27	37.3	.027	.026	100/70	+ 2
4	A*	448	33.6	0.11	13.6	.079	.016	94/88	−22
	P	617	80	0.18	32.7	.015	.019	90/46	+ 9

* Had received 1 grain of thyroid extract daily for 5 days prior to this observation.

Legend: Effects on renal function, basal metabolic rate and arterial blood pressure of treatment of 2 patients (*Nos. 1 and 2*) suffering from hyperthyroidism and 2 (*Nos. 3 and 4*) suffering from myxedema. The rates of renal blood flow, glomerular filtration, secretory capacity are expressed respectively in cc. of plasma and mg. diodrast-iodine per minute per 1.73 square meters of surface area. Resistances (R_A = afferent, R_E = efferent) are calculated by the method of Lamport (8).

Hyperthyroidism. The absolute levels of the plasma clearances and of Tm_D were within normal limits at the first observation. In one patient (*No. 1*) restoration towards normal of the B.M.R. from plus 83 to plus 14 per cent by thyroidectomy did not significantly change the rates of renal blood flow and glomerular filtration, although the filtration fraction was somewhat increased. Renal vascular resistance was unchanged. Postoperatively, Tm_D was diminished by 10 per cent. In the other patient (*No. 2*) a decrease of the B.M.R. from plus 58 to plus 19 per cent was associated with a moderate decrease in renal blood flow, and increases in filtration fraction and diastolic arterial pressure. These changes were accompanied by an increase in renal vascular resistance. The pattern of renal function is consistent with that of essential hypertension. Tm_D was decreased by about 12 per cent.

Myxedema. An increase in basal metabolism from minus 31 to plus 2 per cent in one patient (*No. 3*) was associated with an 18 per cent increase in renal blood flow, an 83 per cent increase in glomerular filtration rate and an increase in the filtration fraction. The function most affected was Tm_D which increased 236 per cent. In the second patient of this pair (*No. 4*) a change in B.M.R. from minus 22 to plus 9 per cent was accompanied by a 38 per cent increase in renal blood flow, a greater increase in filtration rate (+138 per cent) and a 140 per cent increase in Tm_D. It should be noted that this patient had been under treatment with desiccated thyroid for five days at the time of the first observation.

In spite of the restoration towards normal of the basal metabolism in these two patients and the associated clinical improvement, the absolute and relative levels of renal blood flow had not returned to normal at the time of the second observation. In both also, treatment resulted in a decrease of the renal vascular resistance R_A which measures resistance from the aorta to the end of the glomerular capillaries.

DISCUSSION

Hyperthyroidism. Surprisingly, the rates of renal blood flow, glomerular filtration and tubular secretory capacity (Tm_D) are not increased in proportion to the increase of basal metabolic rate. The changes (−10, −12 per cent) in Tm_D postoperatively probably reflect decreases in renal cellular metabolism. However, the degree of these changes just exceeds the limits of reproducibility of the procedure (5). Hyperthyroidism, at least in these two patients, was not associated with renal vasodilation comparable to that which occurs in the extra-renal circulation, nor does it greatly alter tubular secretory capacity. Experimentally, administration of thyroid extract to normal dogs increases plasma diodrast clearance by only 5 per cent, while Tm_D increases by nearly 50 per cent (7). An increase in Tm_D of

115 per cent has been observed in a dog given thyroxin (6). Tm_D is evidently more altered by experimental than it is by clinical hyperthyroidism.

Myxedema. The sluggishness of function in this condition is reflected in decreases below normal levels of renal blood flow, glomerular filtration and Tm_D. Treatment with desiccated thyroid increases renal blood flow, roughly in proportion to the increase in basal metabolism. Glomerular filtration rate is disproportionately increased, apparently as the result of vasodilation in the afferent vascular tract, possibly of the afferent arterioles. The changes of urea clearance found in myxedema by Beaumont and Robertson (2) are thus seen to reflect changes in glomerular filtration. Treatment also causes a disproportionately great increase in Tm_D. This effect is especially noteworthy when the relative changes of Tm_D and B.M.R. in myxedema are compared with those in hyperthyroidism.

The increase in Tm_D observed as the result of treatment of myxedema is probably not an expression of increased tissue metabolism resulting from stimulation by thyroid hormone. On the one hand, the increase greatly exceeds the degree of concurrent changes in B.M.R. and, on the other, the changes of Tm_D in hyperthyroidism are comparatively slight. Alternatively, the decrease of Tm_D found in myxedema and its restoration towards normal on treatment, may reflect the depressing effect of myxedema and the stimulating effect of treatment on the eosinophilic cells of the anterior hypophysis. It has been suggested (1) that these cells exert a trophic influence on renal tubular secretory function. Hypophysectomy in dogs greatly decreases Tm_D (12) and treatment with anterior lobe extracts increases this function (7). Thyroidectomy in rats decreases the size and number of eosinophilic cells, the change being proportional to the reduction in thyroid tissue (11). It is therefore suggested that the depression of renal function present in some patients with myexdema reflects in part a functional depression of the anterior hypophysis rather than a direct lack of thyroidal hormone.

SUMMARY AND CONCLUSIONS

Observations of specific renal functions in 2 patients suffering from hyperthyroidism, 1 treated by subtotal thyroidectomy and the other with thiouracil, indicate that this condition is not associated with a significant renal vasodilation or with an increase in tubular secretory capacity for diodrast which is proportionate to the elevation of the basal metabolic rate.

Observations in 2 patients suffering from myxedema and treated with desiccated thyroid demonstrate before treatment reductions of renal blood flow, glomerular filtration and tubular secretory capacity. Treatment results in restoration of these functions towards normal. The changes thus induced in renal blood flow and glomerular filtration rate reflect a

decrease in afferent vascular resistance. The depression of tubular secretory capacity in myxedema is excessive in relation to the reduction of basal metabolic rate in this condition and to the changes observed in this function during hyperthyroidism. It is suggested that the renal functional depression present in myxedema is in part a reflection of depression of anterior hypophyseal function rather than a direct renal lack of thyroidal hormone.

PROTOCOLS

Patient No. 1. J. R., a woman aged 67, showed symptoms of hyperthyroidism, (weakness, weight loss, nervousness, tremor, eye signs and elevated basal metabolic rate) in 1939, at which time she was treated by administration of iodine, vitamins, high caloric diet and irradiation of the thyroid gland. Symptoms recurred in 1943 and, after partially effective medical treatment with renewed irradiation of the gland, operation revealed colloid and fetal adenoma. The after-treatment observations recorded in Table 1 were made three weeks after subtotal thyroidectomy.

No. 2. M. W., a woman aged 72, complained of weakness, palpitation, nervousness, and weight loss increasing for one year. Examination revealed tremor, exophthalmos, positive eye signs and increased perspiration with heat intolerance. The initial observation was made November 26, 1943. She was placed on thiouracil 0.2 Gm. twice daily and the dosage gradually increased to 0.4 Gm. three times daily, on which dosage she was maintained. The after-treatment observation was made March 3, 1944. High caloric diet with vitamin supplements was given throughout the treatment period.

No. 3. M. T., a woman, aged 43, had noted weakness, cold intolerance, transitory psychosis and gain in weight over one year. Examination showed the typical appearance of myxedema, confirmed by electrocardiogram and basal metabolic rates. Treatment was begun with ½ grain daily of desiccated thyroid, increased to 3 grains and later decreased to 2 grains daily on which latter dose she was maintained at the time of post-treatment observation. This observation was made 3 months after beginning treatment.

No. 4. C. B., a man aged 47, had myxedema, diagnosed from weakness, slowness of thought, speech and action, cold intolerance, appearance and basal metabolic rate (−40 per cent) in 1938, at which time he was treated with desiccated thyroid. In June, 1943, he was brought to the hospital in toxic delirium with paranoid trends. His appearance was typical of myxedema. The history, obtained from his wife, revealed that he had ceased taking thyroid extract some weeks before admission. Because of his greatly depressed state and inability to cooperate or retain food, treatment was begun at once, the first observations of basal metabolic rate and renal function being made after five days administration of thyroid extract, 1 grain daily. His condition gradually improved and the psychosis disappeared under treatment. The post-treatment observation was made two months after his admission.

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REPORT OF A CASE SHOWING CONGENITAL DEFECTS, SHORT STATURE, RETARDED SEXUAL DEVELOPMENT AND NO URINARY GONADOTROPINS

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THE following case is presented because we believe that any differences and variations from the so-called "clear cut case" should be recorded in the literature.

CASE REPORT

In December 1943, a Polish girl, *S. S.*, 16½ years old, came to the Children's Endocrine Clinic with the complaint that she had not grown in height since the age of twelve, and that she had never menstruated nor had she developed any secondary sexual characteristics.

The patient was the fifth in a family of six children. Her mother and four sisters all had a normal menstrual history and apparently were sexually well developed. There was no history of any gross endocrine dyscrasia in any of the immediate family. The patient had had the ordinary childhood diseases. She had been alert mentally and showed good progress at school. Her infantile developmental history pertaining to holding head erect, teething, sitting up, walking and talking, was normal. The patient thought that her linear growth from birth to the age of twelve years seemed to keep pace with that of her friends of similar age. At the age of twelve, however, she noted and was told that her growth had become retarded and soon it became stunted. She also noted that she failed to develop any sizable amount of breast tissue, that pubic or axillary hairs d d not appear, and that she never menstruated.

Physical Examination:

At the time of the first examination on December 27, 1943, she presented a short stature, obesity, a webbed neck and a lack of secondary sexual characteristics (Fig. 1). There was an absence of breast tissue, and an absence of pubic hairs, except for the presence of a few on the labia majora. The labia minora were small and hypoplastic. By rectal examination the body of the uterus could not be delineated, but a small hypoplastic cervix could be felt. In addition, it was found that the teeth were carious and showed malpositions and malocclusions. The eyes revealed a slight exophthalmos, a normal fundus and no abnormal ocular muscle palsies. The ring finger of her right hand was congenitally foreshortened. Her weight was 130 pounds and her linear height 54 inches. She presented eunuchoid skeletal proportions.

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Laboratory Data:

The fasting blood sugar was 94 mg. per 100 cc. and the total cholesterol was 300 mg. per 100 cc. of blood. There were no abnormalities in a casual urine examination. The Wassermann test was negative and the basal metabolic rate was minus 26 per cent. A sugar tolerance test (Exton-Rose) showed a fasting blood sugar of 95 mg.; the first sample thereafter was 119 mg. and the second sample was 96 mg. (This is indicative of a hypoglycemic curve.)

Roentgenograms of her skull showed no evidence of increased intracranial pressure;

FIG. 1. *S. S.*, age 16½ years. Note webbed neck, absence of breast development and pubic hair.

the sella turcica was within normal limits in size and there were no erosions of the floor or clinoid processes. Her cervical spine showed no fusion of the intervertebral discs (a Klippel-Feil syndrome was ruled out). There was a congenitally elongated second cervical vertebra which showed a tendency to forward subluxation. Roentgen ray examination of her carpus showed a delay in the closure of the epiphyses of the phalanges and the other epiphyses; a rudimentary small fourth metacarpal bone was noted. The tibia and fibula showed no evidence of periosteal changes. Roentgenograms of the chest showed no abnormal finding of the heart or lungs; there was no coarctation of the aorta.

Hormonal assays were made of the patient's urine for urinary gonadotropins, estrogens and 17-ketosteroids. Urinary gonadotropins (hypophyseal follicle-stimulating hormont, or F.S.H.) were tested according to the modification of Zondek's technique (4) by Kurzrok and Miller. This test is a qualitative one, and if positive, indicates the presence of at least 100 M.U. of F.S.H. per liter. A negative response to this test is found in normal females during the reproductive age. A positive test would indicate that there were increased urinary pituitary gonadotropins. According to the method outlined above, which was used on two different occasions and performed in two different laboratories, our patient showed no perceptible urinary pituitary gonadotropins either before or after three years of hormonal therapy. Urinary estrogens were measured according to the acid hydrolysis method of Smith and Smith (6). Here, results would indicate that normal women should excrete 4 to 20 R.U. in 24 hours. Our patient showed only slight traces of estrone. Neutral 17-ketosteroids in the urine were determined by the colorimetric method of Sachs and Kurzrok (3). Normal values by this method range from 2 to 5.6 mg. in 24 hours in the adult female. Our patient showed a normal value of 3 mg. in 24 hours.

Treatment:

Varied hormonal therapy,[1] which included estrogens, progesterone and thyroid, was instituted. Three years of treatment produced no perceptible changes either in height, sexual development or in urinary gonadotropins.

DISCUSSION

Since 1938, when Turner (7) reported 7 cases with the "Syndrome of infantilism, congenital webbed neck and cubitus valgus," there have been accumulating in the literature quite a few reports of cases like ours. Varney, Kenyon and Koch (8) in 1942 called it "Association of short stature, retarded sexual development and high urinary gonadotropin titers in women: ovarian dwarfism." Albright and his colleagues (1) in 1942 called it "A syndrome characterized by primary ovarian insufficiency and decreased stature." Schneider and McCullagh (5) in 1943 used the term "Turner's syndrome"; Wilkins and Fleischmann (9) in 1933 called it "Ovarian Agenesis," and only recently E. B. del Castillo et al. (2) called it a "Syndrome of rudimentary ovaries."

From their reports it was apparent that all were describing cases characterized principally by shortness in stature, hypoplastic genitals, primary amenorrhea, an absence of secondary sexual characteristics, congenital abnormalities of skeletal structure, diminished 17-ketosteroids, an insufficiency of estrogens, and increased pituitary follicle-stimulating hormone (F.S.H.) or urinary gonadotropins.

Our case differed in that there was found to be an absence of follicle-stimulating hormone, a trace of estrone, and normal 17-ketosteroids, as shown by tests made at two laboratories on two different occasions. Wheth-

[1] We are indebted to Dr. Stoner of the Schering Corporation for a liberal supply of Progynon B, Proluton and Prometron.

er this places our case in a subgroup of the syndrome described by the other investigators remains to be seen and depends upon whether other such cases with similar assays are found.

In spite of the variations in our case which may place it in a subgroup, we, like some of the other investigators, think that the cause of this syndrome is genetic. Further, we believe that one of the congenital defects is an involvement of the gonads to a marked degree and a moderate involvement of the anterior pituitary gland. The marked involvement of the ovaries would account for the genital defects and open epiphyses; and the moderate involvement of the anterior pituitary gland would account for the stunting instead of dwarfism. It would perhaps also account for the absence of urinary gonadotropins.

SUMMARY

This report covers the case of a 16½ year old girl with stunted growth, primary amenorrhea, no secondary sexual characteristics, obesity, a delay in osseous status as evidenced by open epiphyses, and in addition such characteristic congenital defects as webbed neck and cubitus valgus.

Hormonal assays showed only traces of estrone, normal 17-ketosteroids and an absence of urinary gonadotropins (F.S.H.) rather than the usual absence of estrone, low 17-ketosteroids and an excess of urinary gonadotropins.

If, in the future, other cases with findings such as ours occur, it is likely that these might be considered a subgroup of this syndrome, which was originally described by Turner.

We think that the cause for the syndrome in our case is in all likelihood genetic. Further, we believe that among the congenital defects manifested, one is an involvement of the gonads to a marked degree, and another a moderate involvement of the anterior pituitary gland which would account for the endocrine symptoms.

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THE TREATMENT OF THYROTOXICOSIS WITH AMINOTHIAZOLE—RESULTS IN TWENTY-THREE CASES

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IT is our purpose in this report to present the results of treatment with aminothiazole in 23 cases of thyrotoxicosis. This compound (Fig. 1) appears to have been first used clinically in the treatment of thyrotoxicosis in France in 1943 (9), following the observation of goitrogenesis and improvement of thyrotoxic symptoms among workers in chemical plants who were exposed to the compound. Perrault and Bovet (10) and other French writers (3, 4, 6) have reported satisfactory results from the use of aminothiazole in thyrotoxicosis, but their data are not susceptible to critical

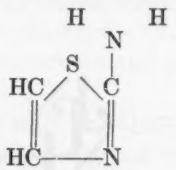

FIG. 1. Aminothiazole.

analysis. The only report of its clinical use which we have found in the American literature is that of Williams (11), who employed it in 9 cases. One patient developed jaundice and another dermatitis, fever and arthritis while under treatment. Williams lists this compound as of low clinical potency and desirability among antithyroid drugs. The goitrogenic and antithyroid action of aminothiazole in the rat was found by Astwood and others (2) to compare with that of thiouracil in the ratio of 0.15 to 1.00. Astwood (1) also reported its antithyroid activity in the rat to be less than that of thiourea. Like many other goitrogenic compounds it inhibits, in a manner not yet clear, the synthesis of thyroid hormone within the gland.

Our 23 cases fall into two groups—9 patients who were given aminothiazole in preparation for thyroidectomy, and 14 in whom treatment was begun with the hope of producing a prolonged or permanent remission without operation. Data relating to the first group are presented in Tables 1 and 2. It will be seen that withdrawal of therapy was necessary because

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of toxic or sensitivity reaction in 5 cases before any effect was noted. One of the 4 patients who received aminothiazole during the entire preoperative period was also given iodine for 13 days prior to thyroidectomy. This iodinization was necessary because the patient was becoming increasingly disturbed emotionally as a result of her failure to enter a remission after 38 days on aminothiazole. No significant change was noted in the size or consistency of the thyroid glands of these 4 patients. At operation the glands were somewhat firm rather than friable, and hemorrhage was not

TABLE 1. DATA RELATING TO PATIENTS TREATED WITH AMINOTHIAZOLE

	Preoperative Use	Prolonged Use
a. Sex		
Males	2	2
Females	7	12
b. Goiter type		
Diffuse	7	14
Nodular	2	0
c. Previously treated	3	7
d. Basal metabolic rate (Initial range)	+25 to +69 per cent	+23 to +65 per cent
e. Daily dosage	0.6 gm.	Initially 0.6 gm. Maintenance 0.1–0.2 gm.

troublesome. The postoperative course was uneventful in these patients. Histologic sections from the 2 toxic diffuse goiters showed considerable variation in different areas. Rather marked increase in colloid content and flattening of acinar epithelium, comparable to the changes produced by iodine, appeared interspersed among areas showing little colloid and marked epithelial proliferation of columnar type. Neither of these patients had received iodine.

Similar variation from moderate hyperplasia of acinar epithelium with diminished colloid content, to marked increase in colloid acinar content with flattened cuboidal epithelial cells was observed in the two toxic nodular goiters. The goiter of one of these patients, who had received iodine in addition to aminothiazole for the last 13 days of the preoperative period, also showed marked fibrosis and areas of calcification and old and recent hemorrhage. The histologic changes in these 4 goiters differ from those observed in patients treated with thiouracil, in that the degree of hyper-

plasia and vascular engorgement was less intense and uniform in the former.

Eight of our patients were subjected to thyroidectomy following iodinization, at intervals varying from 9 to 45 days after aminothiazole had been stopped because of untoward reactions. Aminothiazole had been given to these patients for periods varying from 8 to 30 days. One patient

TABLE 2. RESULTS OF PREOPERATIVE USE OF AMINOTHIAZOLE (9 CASES)

Patients satisfactorily prepared	4
Preoperative period	17, 27, 51, 92 days
Patients showing unsatisfactory response (Reactions)	5

was operated upon 8 months after withdrawal of aminothiazole. The histologic appearance of the thyroid glands of these patients showed no significant difference from that usually seen after iodine therapy in toxic goiter, with the possible exception that vacuolization of the colloid was rather prominent.

Data relating to the 14 patients in whom therapy was undertaken in an effort to produce prolonged or permanent remission are presented in Tables 1 and 3. It will be noted that aminothiazole had to be withdrawn in 7 cases because of untoward reactions. Four of these patients were subsequently subjected to thyroidectomy; 2 are still under treatment with

TABLE 3. DATA RELATING TO PROLONGED TREATMENT WITH AMINOTHIAZOLE (14 Cases)

	Minimum	Maximum	Average
Onset of remission (days)	30	75	51
Duration of treatment (months)	2	12	5.9
Sustained remission			
a. Still under treatment			4
b. After treatment was discontinued			3
Unsatisfactory responses (reactions)			7

propylthiouracil, and one who is recovering from an hepato-toxic reaction is receiving no antithyroid treatment at the time of writing. Three of the 7 patients who showed satisfactory response have remained in remission for 8, 8, and 2 months respectively after the drug was stopped. They were treated for 4, 2, and 3½ months respectively. One patient showed a definite decrease in the size of her goiter after 3½ months of treatment. Two pa-

tients (both 13 year old girls) have shown appreciable increase in the size of their thyroid glands after 3 and 4½ months of therapy respectively. No significant change in exophthalmos has been observed in any patient during or after treatment. One patient, a man aged 65 with auricular fibrillation and congestive heart failure, has been kept under satisfactory control with reversal to normal cardiac rhythm and freedom from congestive signs for 7½ months on a daily maintenance dose varying from 0.05 Gm. to 0.2 Gm.

Our usual initial dose of aminothiazole was 0.6 Gm. daily given in three divided doses for adults, and 0.4 Gm. daily for the two children. During preoperative preparation the initial daily dose was not reduced. The basal

TABLE 4. TOXIC AND SENSITIVITY REACTIONS TO AMINOTHIAZOLE

Patient	Duration of Treatment Prior to Onset	Daily Dose at Onset Gm.	Total Dose at Onset Gm.	Type of Reaction	Duration of Reaction
D.C.	9 days	0.6	5.4	Fever	3 days
S.M.	2 months	0.4	30.4	Hepatitis with jaundice	2 weeks
C.A.-G.	15 days	0.6	9.0	Fever, urticaria arthralgia, subcutaneous nodules	acute—1 month chronic—7 months
D.B.W.	9 days	0.6	5.4	Fever, nausea, vomiting	3 days
L.M.	8 days	0.6	4.8	Chills, fever, macular rash	1 month
M.C.	9 days	0.6	5.4	Fever	3 days
J.F.	8 days	0.6	4.8	Urticaria, macular rash	1 week
B.D.	3 months	0.6	38.8	Hepatitis with jaundice	2 weeks
D.L.	11 days	0.6	6.6	Arthralgia, nausea, vomiting	1 week
W.P.	22 days	0.6	13.2	Generalized lymphadenopathy, fever	1 week
D.W.	28 days	0.6	16.8	Arthralgia, fever, urticaria	1 week
H.L.	36 days	0.6	21.6	Intermittent pruritis	10 days

metabolic rate was determined once weekly in hospital patients and every two weeks in outpatients. In patients receiving prolonged treatment the daily dose was gradually reduced as remission occurred; the ultimate daily maintenance dose varied from 0.05 Gm. to 0.2 Gm.

There may have been some correlation between the initial basal metabolic rate and the time required for remission to appear. Thus, in 3 patients with initial basal metabolic rates above plus 56 per cent, remission occurred in an average of 59 days; in 4 patients with initial basal metabolic rates between plus 44 and plus 45 per cent remission appeared in an average of 53 days; and in 3 patients with initial basal metabolic rates of plus 38 per cent or below, the average time required for remission was 42.5 days.

Data relating to toxic or sensitivity reactions are presented in Table 4. *Untoward reactions forcing interruption of therapy occurred in 12 cases, or 52 per cent. These reactions, in descending order of frequency, included:* (1) fever with malaise, sometimes accompanied by nausea and vomiting;

(2) skin eruptions, either urticarial or maculopapular, with severe pruritis; (3) arthralgia, with or without fever and malaise; (4) jaundice with evidence of hepatic cell damage as demonstrated by liver function studies; (5) pruritis without skin eruption; (6) generalized lymphadenopathy. Reactions appeared in from 8 to 90 days after treatment was instituted, the average time being 25.5 days. Reactions appeared in 15 days or less in 7 of the 12 patients. Jaundice appeared in 2 patients, 60 and 90 days respectively after beginning treatment, with respective total doses of 30.8 Gm. and 38.8 gm. of aminothiazole. Both of these patients were more jaundiced than ill, although evidence of hepatic damage was obtained by liver function studies in each case. Arthralgia occurred in 3 cases. In 2, it was of brief duration and involved the hands, wrists, elbows and shoulders. The third patient was of unusual interest as the following protocol will show:

CASE REPORT

Mrs. C. A-G., a white married woman, aged 30, was admitted to the Surgical Division on October 30, 1946, with a diagnosis of toxic diffuse goiter. Her symptoms, which were typically those of thyrotoxicosis, had begun in May 1943, following the neonatal death of her first child. The previous medical history was irrelevant. On admission she presented a typical picture of toxic diffuse goiter with slight exophthalmos and moderate diffuse enlargement of the thyroid. The basal metabolic rate was plus 69 per cent. Preoperative medication was begun with aminothiazole 0.2 Gm. three times daily. Evidence of remission of the thyrotoxicosis was only slight during the first two weeks. On the fifteenth day of treatment an urticarial eruption appeared over the extensor surfaces of the knees and elbows. This spread rapidly until it involved most of the trunk, extremities and face, and was accompanied by pruritus and recurrent bouts of angioneurotic edema. Aminothiazole was discontinued at the onset of the urticaria. Two days later severe pain and swelling appeared in the knees, wrists, and elbows, accompanied by a rise in temperature to 103.6° F., extreme malaise and collapse. Subsequently the shoulders, hands, and jaws were involved and reddish tender indurated areas appeared over both arms and legs. These varied in diameter from about 1 to 4 cm. and subsided slowly over a period of 2 to 3 weeks. The patient was very ill and movement of the involved joints caused excruciating pain. The total leucocyte count did not rise above 10,000 per cubic mm. and the eosinophiles varied from 0 to 6 per cent. Cultures from throat, urine and blood stream revealed no pathogenic organisms. Irregular and gradually subsiding fever continued with slow improvement in joint and cutaneous manifestations for about 23 days, at which time the patient was fairly comfortable except for some residual pain and stiffness in knees, shoulders, elbows and wrists. Iodinization was begun 9 days after the onset of the urticaria and 25 days later a subtotal thyroidectomy was performed with an uneventful postoperative course. The patient has been followed for 6 months since operation. There has been no recurrence of the thyrotoxicosis. Stiffness, slight swelling and intermittent pain have recurred with decreasing frequency and severity in the previously affected joints. Minor urticarial outbreaks with slight swelling of the face and eyelids have recurred occasionally. The sedimentation rate of the red cells has remained within normal limits throughout. Roentgen rays of the affected joints have shown nothing abnormal. The entire episode seems to be attributable to the aminothiazole and the persistence of symptoms is noteworthy.

The reactions involving fever, malaise, gastrointestinal disturbances, and maculopapular skin eruptions subsided within 7 days except in the case of one patient who showed persistent fever and grippe-like symptoms for two weeks. The total leucocyte count declined by 1000 cells or more per cubic mm. in 8 patients during treatment. The lowest leucocyte count was 3900 per cubic mm. Neutropenia did not occur in any case.

Morgans (7) reported the following reactions in 13 patients treated with aminothiazole:

Drug fever	6
Rashes	5
Adenopathy	1
Jaundice	2
Nausea and vomiting	3

Perrault (8) reported the following incidence of reactions in 129 cases: digestive disturbances, including jaundice (5 per cent); oliguria with lumbar pain (incidence not stated); fever and malaise (7 per cent).

Perrault and Bovet (10) mention the occurrence of a pinkish discoloration of serum and urine by aminothiazole but we did not observe this in any of our patients.

Eckfeld, Seifter et al. (5) were able to recover only traces of aminothiazole from the blood and urine of 4 of our patients who had taken the drug for 5, 6, 7 and 7 weeks respectively in doses of 0.8 Gm., 0.2 Gm., 0.6 Gm., and 0.4 Gm. daily. They had a similar experience with dogs which had but recently received large doses of the drug, and concluded that attempts to adjust dosage by determining blood levels were futile. They produced fatal poisoning in dogs, with severe hepatic damage, both by single doses of 250 mg. per kg. and repeated doses of 60 to 80 mg. per kg. of body weight.

It is possible that a distinction should be drawn between toxic and sensitivity reactions in those patients who exhibited intolerance to aminothiazole. The transitory arthralgias, adenopathy, fever and cutaneous manifestations may well have been phenomena of sensitivity. The objective evidence of hepatic damage found in our 2 jaundiced patients, however, suggests a direct toxic effect on the liver. The prolonged joint symptoms described in our patient, C. A-G., suggest that the drug may in this case have initiated a series of events which should be considered more than simply phenomena of drug sensitivity.

It is apparent that the results of treatment of thyrotoxicosis with aminothiazole in the doses employed in our small series of cases do not compare favorably with those attainable either by subtotal thyroidectomy or by such antithyroid compounds as thiouracil and its derivatives. The high incidence of untoward reactions alone would seem to render this substance impractical for clinical use. In view of Astwood's report (2) that the anti-

thyroid action of aminothiazole in the rat was only about $\frac{1}{8}$ that of thiouracil, it may be asked whether we should have employed larger doses. The occurrence of undesirable reactions in 52 per cent of our patients, including 2 with hepatic damage, would appear to be sufficient answer to this objection.

SUMMARY AND CONCLUSIONS

1. The results of the administration of aminothiazole[1] to 23 patients with thyrotoxicosis have been reported.

2. Toxic or sensitivity reactions sufficient to warrant withdrawal of treatment occurred in 12 patients (52 per cent). Two patients became jaundiced with evidence of hepatic damage. One patient showed an unusually prolonged reaction characterized by arthralgia and urticaria recurring for 7 months.

3. Three patients were successfully prepared for thryoidectomy with aminothiazole alone. At operation the consistency of their thyroid glands was firmer, and the glands less friable, than is usually the case in patients prepared with thiouracil or its derivatives.

4. Three patients have remained in remission for from 2 to 8 months following withdrawal of the drug.

5. Aminothiazole appears to possess no advantages over thiouracil compounds in the treatment of thyrotoxicosis, and its marked tendency to produce toxic or sensitivity reactions would appear to preclude its clinical use.

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IODINE-LACK THEORY AND ENDEMIC GOITER

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THE article on lack of iodine and endemic goiter by Greenwald (8) and the heated commentaries that followed its publication prompt me to comment on the contents of this publication and its criticisms and to discuss briefly the problem in question.

In 1932, I published a monograph of 60 pages, concerning goiter and the iodine-lack theory (26) which critically surveyed the world literature on this problem and contained a series of original investigations into the iodinization of some goitrous and nongoitrous districts in Germany. Strangely enough, Greenwald did not refer to this publication which is based on most of the material he himself used and in which I came to some of the same conclusions about the iodine-lack theory.

Greenwald has, I believe, confounded the issues considerably. On the other hand, his critics have dealt with his article in a highly emotional manner. As the inconsistencies which I noted when revising the then available evidence for and against the iodine-deficiency theory are not unlike some of Greenwald's observations, I feel entitled to take part in the discussion which has arisen out of his recent publication.

Greenwald has been unfortunate enough to connect the question as to whether lack of iodine is the cause of endemic goiter with the theory and the results of *iodine prophylaxis* of which he says that "in some cases there has been no effect at all, or even an increase in the incidence" (of goiter). He also mentions that the "changes in the virulence in the disease" may have been mistaken for the results of the prophylactic use of iodine which "has not reduced the incidence of new goiters to zero." Although the literature on the etiology of endemic goiter reveals the complexity of the problem, the general opinion about the value of iodine prophylaxis appears to be uniform, and the published results which, by now, extend over more than two decenniums, leave no doubt that the administration of iodine represents an important preventive method against endemic goiter. It seems therefore unjustified and unwise to use criticisms against the value of iodine prophylaxis as an argument against the iodine-lack theory, because neither good nor bad results obtained with the prophylactic administration of iodine are a proof for or against the theory that endemic goiter is caused by lack of iodine. Also, this simple logic has unfortunately not been fully realized by the champions of iodine prophylaxis. Many of them have at the

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same time become the most ardent protagonists of the iodine-lack theory, while other workers in this field are still of the opinion that "simple iodine-lack is no doubt not the whole story" (Iodine and Goitre. *Lancet*, 1: 754, May 31, 1947). Kimball (16) does not agree. The summary of his paper, read at the Third International Goiter Conference, begins as follows:

"We have definitely proven that:

(1). Simple or endemic goiter is a deficiency disease and this deficiency is iodine in our food and drink . . .

(2). The addition of an exceedingly small amount of iodine to our food in endemic goiter regions prevents goiter . . . "

It should be clear to everyone that 2) can be true even if 1) is a fallacy, and the scientists on councils and committees who are occupied with the introduction of iodine prophylaxis of endemic goiter need not be alarmed, should the iodine-lack theory prove to be wrong. Many discoveries in medicine were based on wrong theories which have since proved useful or even revolutionizing. This has not prevented anyone in the past from revising the bases of such discoveries and from uncovering any erroneous propositions, and we hope that, in spite of interference by agencies and the daily press, the same attitude will also prevail in the future, should a similar occasion arise.

The second point which demands clarification is the iodine-lack theory itself. Here again, Greenwald's conclusion that endemic goiter is not due to a lack of iodine does not seem precise enough, as it does not distinguish between the two aspects of the iodine-lack theory. Chatin (4) who first introduced it on a scientific basis has formulated it as follows:

1. Le goitre et le crétinism sont inconnus dans les contrées normalement iodurées (Goiter and cretinism are unknown in districts with a normal iodinization).
2. Ces maladies se montrent quand la proportion de l'iode diminue (These diseases appear when the proportion of iodine diminishes).

According to Chatin's conception the iodine-lack theory, of endemic goiter means that goiter and cretinism are due to an insufficient iodinization of the district (=primary exogenous lack of iodine), a fact he thought to have proved by iodine analyses of water, food, soil, air, derived from goitrous localities. A commission, appointed by the French Academy to investigate Chatin's claims, failed to confirm his results in 1852, and the theory fell into disrepute until McClendon et al. (21) in America (1923) and von Fellenberg (6) in Switzerland (1923–26) revived it on the strength of new iodine assays by means of a more modern microtechnique.

On the other hand, students of thyroid physiology and pathology who have investigated the relationship between iodine and thyroid function since Baumann's discovery that iodine is a normal constituent of the thyroid (1896), have been led to the conclusion that goiter formation and io-

dine metabolism are linked together. Since it has been shown that goiter represents a compensatory hypertrophy, the hypothesis was put forward that "the immediate cause of goiter is failure of the thyroid gland to obtain an adequate supply of iodine" (Harington (9)) or, as Marine (18) formulated it earlier, that "the immediate cause of thyroid enlargement is a relative or an absolute deficiency of iodine." Thus, the iodine-lack theory contains two distinct problems, and the questions that have to be answered are:

1) Is the immediate cause of goiter an inadequate supply of iodine to the thyroid gland?

2) If so, are goitrous districts inadequately iodinized and is this the cause of a deficient iodine supply to the thyroid gland?

Both questions have been critically discussed by Greenwald and answered in the negative, but I feel that the distinction between them has not been made clear enough, especially as over half of his paper is devoted to question 2). His conclusion that endemic goiter is not due to lack of iodine may mean that lack of iodine does not lead to goiter formation, or that deficient iodinization of the locality does not, or that both do not. Much depends on the precise answer to these questions.

Regarding the first, which represents the iodine-lack theory in its widest aspect, I think most workers will agree that lack of iodine may play a part in the pathogenesis of goiter, but that we still do not understand the whole problem of goiter formation and are unable to say with certainty how important iodine deficiency is and what other factors are involved. The occurrence of sporadic as well as endemic goiter and the difference in structure between the goiters in mountainous and non-mountainous regions suggest that there may be more than one causative factor. The more recent discovery of goitrogenic factors in plants and of the goitrogenic action of synthetic thiourea derivatives point to a possible role of goitrogenic substances as primary agents which may, however, owe their goitrogenic activity to an interference with the utilization of iodine by the thyroid gland. Animal experiments with iodine-poor diets and attempts to prevent this dietary goiter by the addition of small doses of iodine have not given conclusive results. Goiter can be experimentally produced by different other factors, such as exposure to cold, high protein or fat diet, starvation, and excess of calcium. Iodine-poor diets seem to produce goiter more easily when there is an excess of calcium in the diet; iodine deficiency alone is often followed by atrophy of the gland (Hellwig (11) Thompson (25) etc.). All these observations throw doubts on the correctness of hypothesis 1). The discovery of definite goitrogenic substances which act regardless of the amount of iodine intake, though perhaps by interfering with the utilization of iodine by the thyroid, is especially important. There is little evi-

dence for Kimball's conclusion that it has been "definitely proven that simple or endemic goiter is a deficiency disease and this deficiency is iodine in our food and drink." I venture to say that there is a certain amount of evidence indicating that this is not so. In any case, we need further evidence before hypothesis 1) can be regarded as a fact.

A great deal of work has been done to prove the correctness of hypothesis 2) which represents an older and more specific form of the iodine-lack hypothesis. Here Greenwald's analysis of the facts seems to me worth considering and follows lines similar to my own (1932). The reasons against the validity of this form of the iodine-lack theory are partly methodical, partly based on the actual results gained from iodine estimations of soil, water and food that were meant to show the existence of an inverse correlation between goiter incidence and iodinization of the locality. The conclusions which I drew in the quoted monograph ((26) p. 426) seem to me as correct today as at the time they were written. It would be sufficient to quote them again without further comment, but on account of the highly controversial nature of the problem it seems more appropriate to give a brief account of the reasons which led to their adoption. Details have to be looked up in the publication itself and can also be found in Greenwald's paper.

1) There can be no doubt that the methods used for iodine analyses of foodstuffs etc. were not only unreliable but that the error exceeded any permissable error of a biochemical microanalytical method. I worked with von Fellenberg's original method (6) about which criticism was raised by the author himself as late as seven years after the introduction of the method (quoted by Ucko (26) p. 375). On the other hand, von Fellenberg was unable to obtain satisfactory results with McClendon's method (21) and also criticized various modifications of his own method which were introduced later on. In fact, it is no exaggeration to say that the greater part of the published results on iodine estimations in various materials may be methodically wrong, and it appears even doubtful whether the error is constant enough to compare the results obtained by the same author in his different analyses. To give an example of the situation I have tabulated the figures which different authors have obtained in analyzing the iodine content of bread and potatoes in goitrous and nongoitrous districts of various parts of the world. (See Table 1.) The figures vary between 8 and 115 micrograms for bread and between 8 and 85 micrograms for potatoes in non-goitrous localities alone. If one compares the figures for goitrous and non-goitrous districts with each other, one can easily see that they overlap considerably and that a decisive difference is only evident if the figures of the same author are compared. The same is true if the figures for other foodstuffs, soil, water, etc. are compared in this way.

TABLE 1. IODINE CONTENT OF BREAD AND POTATOES IN DIFFERENT DISTRICTS
(micrograms per kilogram)

District	Bread		Potatoes		Authors
	Non-goitrous	Goitrous	Non-goitrous	Goitrous	
Argentine					
Buenos Aires	—		32		Mazzocco (19)
Salta		—		12–20	Mazzocco (19)
New Zealand	12		22		Hercus (12) (13)
Switzerland			31	17; 35	Fellenberg (6)
La Chaux-de-Fonds	16		18		Fellenberg (6)
Signau (cf. p. 7)		8		11	Fellenberg (6)
Germany					
Bavaria	75–92	70–76	28	20	Bleyer (2)
Palatinate	102–115		34		Bleyer (2)
Holstein	—		32		Bleyer (2)
Danzig	0		85		Glimm (7)
East Prussia	50		15		Isenbruch (15)
Greifswald	19		7–9		Ucko (26)
Kiel	8		10–13		Ucko (26)
North Friesian Islands	—		15		Ucko (26)
Berlin	28		9–14		Ucko (26)
Kassel Town	61		6–17		Ucko (26)
Kassel County	43	32–39	13	11–13	Ucko (26)
Merseburg County	65	22	8	14	Ucko (26)
Kottbus		43		15	Ucko (26)
Glatz County		27–32		2–18	Ucko (26)
Hungary	44	25	15	5	Bodnar & Straub (3)

2) On reading the evidence for an inverse relationship between goiter incidence and iodinization of the locality, serious doubts arise also about the estimation of goiter incidence. Such statistics have been collected sometimes by the observer himself, sometimes by local authorities, by commissions, etc, and the criteria used vary considerably. As an example of the unreliability of such statistics it may be recalled that one of von Fellenberg's classical findings in favor of the iodine-lack theory was the difference in La Chaux-de-Fonds and Signau in Switzerland, the former be-

lieved to be goiter-free, the latter goitrous. However, Stiner (24) reported in 1927 that goiter occurs in over 50 per cent of school children and in 21 per cent of 20-year-old males in La Chaux-de-Fonds, as compared with 28 per cent of the same age group in Signau. Both places seem therefore to have nearly the same goiter incidence and had to be put into the same group in Stiner's goiter map of Switzerland. Such happenings throw serious doubts on the reliability of the iodine estimations and show how careful one should be in drawing conclusions from available data.

3) There seems to be no doubt that certain regions in which goiter occurs endemically, are rich in iodine (1, 14, 17, 20) and that endemic foci occur in districts near the sea where a high iodinization of the locality definitely exists. If endemic goiter were a "deficiency disease" caused by insufficient iodine supply and if this were the only possible cause of endemic goiter, such occurrences would be completely impossible.

4) Although a number of workers have found less iodine in foodstuffs, soil, water, etc. in goitrous than in non-goitrous regions, a comparison of figures does not show that the lower the iodinization of the district, the higher the incidence of goiter. This inverse relationship should, however, be unmistakable if goiter was due to deficient iodine intake because of insufficient iodinization of the district. I therefore agree with Greenwald, that a primary exogenous iodine deficiency has not yet been sufficiently proved. Attempts have been made to calculate the daily iodine intake by estimating the amount of iodine present in a theoretical daily menu. A few figures from different countries will suffice to show that these figures are also not convincing and cannot prove an exogenous iodine deficiency in goitrous regions. Thus, von Fellenberg estimated the daily iodine consumption in Switzerland to be 60 micrograms in non-goitrous, 20 micrograms in goitrous districts; Lunde's (17) corresponding figures for Norway are 35 and 20 micrograms; I have found from 31 to 53 micrograms in non-goitrous and minor endemic districts of Germany, and Reith (23) found an average daily intake of 150 micrograms in Holland where endemic foci occur in spite of an iodine intake $2\frac{1}{2}$ times that of Switzerland. The possibility of a secondary deficiency remains, though conclusive data are likewise lacking. Secondary deficiency could be produced by a variety of exogenous factors, such as one-sided nutrition, loss of iodine by inadequate preparation of food or certain environmental factors, or it may be caused by endogenous factors such as impaired absorption, increased demands, interference with the utilization of iodine (this may be produced by specific exogenous goitrogenic substances). The cause of endemic goiter, however, must be one which acts generally on all the inhabitants and even on the animals in the district, as it has been shown that the average weight of the thyroid glands

even of non-goitrous individuals is higher throughout life than in non-goitrous districts.

5) It is impossible to say that Chatin's hypothesis that an exogenous lack of iodine is the cause of endemic goiter has been proved. This does not mean that lack of iodine cannot be the cause of goiter, although there seems to be reason to assume that it is not the only cause. It is here that the controversies start, and Greenwald's analysis would perhaps have been received with more positive criticism if he had analyzed the different aspects of the iodine-lack theory instead of refuting it indiscriminately. The whole problem can only be solved by a further analysis of the iodinization in definitely goitrous and non-goitrous districts with a technique that fulfils the demands of a reliable microanalytical method. In the same way, further investigations into the iodine excretion of goitrous and non-goitrous individuals are necessary, whereby the question has to be examined again whether the normal organism is in the state of iodine equilibrium. Greenwald's publication contains a full critical survey of the results obtained so far from estimation of the iodine excretion. Previously published figures by Clark & Adams (5) for Massachusetts, Lunde (17) for Norway, and von Fellenberg (6) for Switzerland, present problems similar to those quoted by Greenwald.

It is hoped that this brief analysis of the available evidence for and against the iodine-lack hypothesis of endemic goiter will help to clarify the matter, to pave the way for further research, and also to show that the iodine prophylaxis of endemic goiter is not affected in any way by etiological theories.

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LETTERS TO THE EDITOR

To The Editor:

THE INTRANASAL USE OF POSTERIOR PITUITARY POWDER IN THE TREATMENT OF DIABETES INSIPIDUS: A REMINDER

THE present limited supply of aqueous solutions of posterior pituitary has become a matter of concern for those patients with diabetes insipidus whose therapy has been based on the injection of this preparation. This circumstance has prompted us to call the attention of those who might be unfamiliar with it to an alternative procedure, namely, the intranasal insufflation of posterior pituitary powder U.S.P., of which the antidiuretic efficacy has been well established and which has the additional advantages of greater convenience and economy.

The initial observations as to the effectiveness of this procedure were made by André and Lucie Choay in 1924,[1] shortly after Blumgart's demonstration of the therapeutic value of the intranasal application of aqueous solutions of posterior pituitary.[2] Their experience has been confirmed by many others, and reviewed and supplemented with additional favorable results by Smith.[3] In spite of such general agreement as to its merits, the intranasal use of posterior pituitary powder has not been as extensive as its effectiveness, convenience and economy would warrant.

A brief summary is given in Table 1 of our own findings as to the relative efficiency of the powder given intranasally, the aqueous extracts subcutaneously, and pitressin tannate in oil intramuscularly, in 7 patients with diabetes insipidus. With the exception of patient *N.B.* whose course of therapy was too brief to permit a satisfactory evaluation, all have been well regulated by the intranasal insufflation of the powder. This is administered by a De Vilbiss spray, number 44, which is small enough to be carried in the pocket or purse and delivers approximately 5 mg. of powder with

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each jet. This method enables the patient to administer the required amount of antidiuretic therapy at appropriate intervals without the inconvenience entailed in the use of a hypodermic syringe. There have been no complaints of significant nasal irritation, despite the uninterrupted use of the powder, in some instances, for as long as 2 years.

TABLE 1

Patient, Age, Sex	Pitressin Subcutaneously		Pitressin Tannate in Oil		Posterior Pituitary Powder by Nasal Insufflation	
	Dosage	Therapeutic Response	Dosage	Therapeutic Response	Dosage	Therapeutic Response
T.K. 48 M	10 U b.i.d. 20 U b.i.d.	Good, for 12 years then poor Poor			1 jet* each nostril t.i.d.	Good
R.M. 63 M			5 U q. 36 hours	Fair	1 jet each nostril 4 i.d.	Good
M.F. 12 F	10 U b.i.d.	Fair			1 jet each nostril t.i.d.	Good
S.S. 16 F			5 U	Poor	1 jet each nostril t.i.d.	Good
N.B. 7 M			5 U q.d. 4 U b.i.d.	Poor Good	1 jet each nostril q. 3 hours	Poor†
M.T. 40 F	10 U 6 i.d.	Poor			2 jets each nostril 4 i.d.	Good
J.W. 15 M					1 jet each nostril t.i.d.	Good

* Each jet equivalent to approximately 5 mg. posterior pituitary powder.
† Therapy for only one week at this dosage level; then stopped.

The cost of therapy with posterior pituitary powder is from $\frac{1}{5}$ to $\frac{1}{8}$ that of parenteral preparations at current retail prices.

ANNE C. CARTER
EPHRAIM SHORR
September 2, 1947

Department of Medicine
Cornell University Medical College and
The New York Hospital
New York City

TO THE EDITOR:

FATAL JAUNDICE RESULTING FROM THIOURACIL

Fatal cases of agranulocytosis as well as non-fatal cases of jaundice resulting from the use of thiouracil have already been reported. The following is perhaps the first reported case of fatal jaundice resulting from the use of that drug.

REPORT OF CASE

G. N., a Spanish businessman, aged 48, had been ill for eight months, complaining of nervousness, palpitation, tremor and marked loss of weight. Examination revealed a diffusely enlarged, non-nodular thyroid and moderate exophthalmos. He also suffered from duodenal ulcer. The patient stated that for some time he had been taking Lugol's solution but without beneficial results. His weight had dropped to 59 kg. The pulse rate was 100, blood pressure 140/75, and the basal metabolic rate +37 per cent. Thiouracil was prescribed and the patient was put on a dosage of 0.6 Gm. daily. After ten days of thiouracil therapy the pulse was 78 and the basal metabolic rate +17.2 per cent. Dosage was repeated for ten more days at the end of which time the pulse was 74 and basal metabolic rate +10 per cent. Inasmuch as the patient's condition had improved a great deal and his weight had increased to 63.2 kg., thiouracil dosage was cut down to 0.4 Gm. daily. White blood cell counts during treatment were normal. Two weeks later symptoms of intense jaundice appeared. Thiouracil was immediately discontinued and treatment with glucose and B complex started at once, with diet and rest. There was not, however, the slightest improvement and the patient died eight days later. No autopsy was allowed but the clinical signs pointed toward acute yellow atrophy of the liver.

COMMENT

The dosage given in this case is no higher than that usually prescribed at present. This confirms the opinion that toxic reactions are not dependent upon the amount of the drug administered. Notwithstanding its recent use, thiouracil has been responsible for some fatalities. The utmost care is required in its administration and it is the author's opinion that it should be employed only in special cases.

LUCIANO DÉCOURT
August 21, 1947

From the Butantan Institute,
São Paulo, Brazil

ANNOUNCEMENT OF THE 1948 MEETING OF THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

The Thirtieth Annual Meeting of the Association for the Study of Internal Secretions will be held in the Palmer House, Chicago, Illinois, June 18 and 19, 1948.

The scientific sessions will be held in the Red Lacquer Room and registration will be on the fourth floor just outside the Red Lacquer Room. The Annual Dinner will be held in the same room on Friday, June 18th at 7 P. M. and will be preceded by a cocktail party, the location of which will be announced later.

All members of the Association who plan to attend the Thirtieth Meeting are urged to make their reservations at once with the Palmer House, stating the time of arrival and how long they plan to remain in Chicago.

Nominations for awards and fellowships of the Association must be in the Secretary-Treasurer's office by March 15, 1948.

Those wishing to present papers should send title and four copies of a comprehensive abstract of not more than 200 words and suitable for publication in the program to Dr. C. N. H. Long, 333 Cedar Street, New Haven, Conn., not later than March 15, 1948.

Announcement of Awards and Fellowship of the Association

Nominations for Awards

Three awards for meritorious work in endocrinology will be given at the next annual meeting of the Association. A special committee of five members of the Association chooses the recipients of these Awards, subject to ratification by the Council, and each member of the Association has the privilege of making one nomination for each award.

Nominations for the Awards should be made on special application forms which may be obtained from the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma. All nominations, accompanied by a statement of the importance of the nominee's contributions to endocrinology and a bibliography of his most important papers with reprints if possible, should be sent to Dr. Turner's office not later than March 15, 1948.

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb and Sons Award of $1,000.00 was established in 1939. It was given in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr. Edward A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori. No award was made in 1943. No age or special limitation is stipulated by the donor of the award.

THE CIBA AWARD

The Ciba Award, established in 1942, is given in recognition of the meritorious accomplishment of an investigator, not over 35 years of age, in the field of clinical or pre-clinical endocrinology. In 1944 the Award was given to Dr. E. B. Astwood; in 1945 to Dr. Jane Anne Russell; in 1946 to Dr. Martin M. Hoffman and in 1947 to Dr. Choh Hao Li. The Award is for $1,200.00. If within two years of the date of the Award, the recipient chooses to use it to aid in working in a laboratory other than the one in which he normally is located, the Award will be increased to $1,800.00.

THE AYERST, McKENNA & HARRISON FELLOWSHIP

The first award of the Ayerst, McKenna & Harrison Fellowship was given to Dr. Samuel Dvoskin in 1947. The fellowship was founded in order to encourage investigation in the field of endocrinology rather than as an award

for work done. The amount of the fellowship is $2,500.00 annually. The nominee must possess the degree of Doctor of Philosophy or Doctor of Medicine or their equivalent. It is suggested that no restriction be placed on age, but that preference be given to applicants who have recently completed the requirements for their Ph. D. or M. D. degree. The nominee must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals; submit a program of proposed study; indicate one or more institutions where the proposed program will be carried out; submit statement of approval from the investigators with whom he proposes to conduct his research; serve full time if awarded a fellowship. A small amount of time (10 to 15 per cent) mat be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

AMERICAN ASSOCIATION FOR THE STUDY OF GOITER

VAN METER PRIZE AWARD

The American Association for the Study of Goiter again offers the Van Meter Prize Award of Three Hundred Dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Toronto, Canada, May 6th, 7th, 8th, 1948 providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten double spaced copy sent to the corresponding secretary, Dr. T. C. Davison, 207 Doctors Building, Atlanta 3, Georgia not later than February 1st, 1948. The committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award Essay by the author if it is possible for him to attend. The essay will be published in the annual Proceedings of the Association. This will not prevent its further publication, however, in any Journal selected by the author.

T. C. Davison,
Corresponding Secretary

Postgraduate Course in Endocrinology

The Postgraduate Committee of THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS, under authority of its Council, announces a course of lectures and demonstrations in CLINICAL ENDOCRINOLOGY to be held in LOS ANGELES at the BILTMORE HOTEL, FEBRUARY 23 to 28, 1948, inclusive.

The faculty will consist of the most prominent investigators and clinical endocrinologists in the various branches of the medical sciences in the United States and Canada.

It is the intent of the Committee that this course be a practical one of interest and value to both the GENERAL PRACTITIONER AND THE SPECIALIST.

A fee of $100 will be charged for the entire course and the attendance will be limited to 100. Registration will be in the order of checks received and will close on February 1, 1948. Should there be an insufficient number of applicants to warrant the course, the registration fee will be immediately refunded in full.

Please make your application on your letterhead and forward, together with your check payable to THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS, to DR. E. KOST SHELTON, CHAIRMAN of the POSTGRADUATE COMMITTEE, 921 WESTWOOD BOULEVARD, LOS ANGELES 24, CALIFORNIA.

Since satisfactory hotel accommodations are still difficult to procure on short notice in Los Angeles, especially during the winter season, it is suggested that all applicants MAKE THEIR RESERVATIONS EARLY.

SOME LARGE HOTELS IN THE METROPOLITAN AREA OF LOS ANGELES:

Alexandria	Chapman Park	Lankershim
Ambassador	Gaylord	Mayflower
Biltmore	Hayward	Town House

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† Abstract of paper presented at the Twenty-ninth Annual Meeting of The Association for the Study of Internal Secretions.

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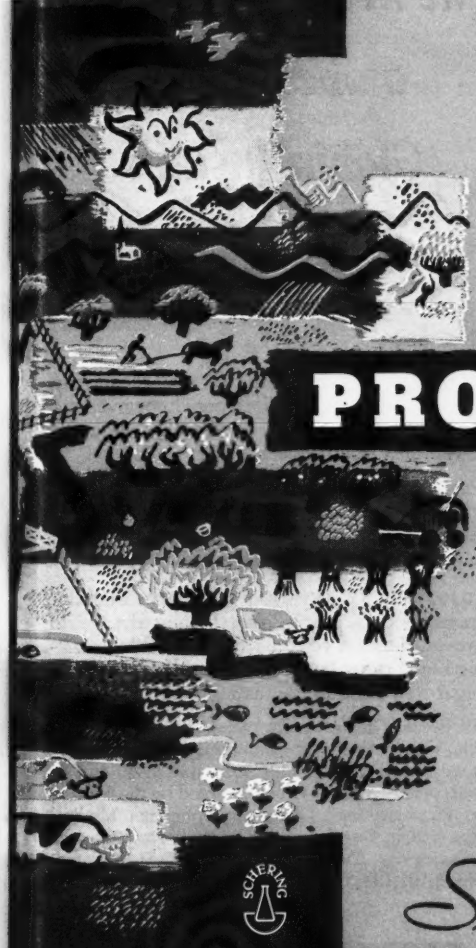

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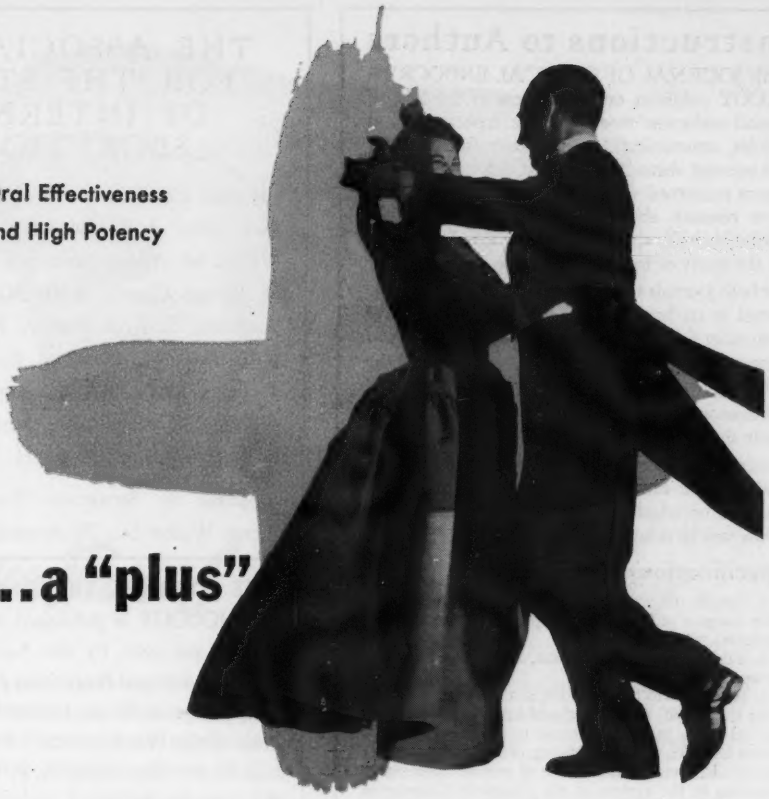

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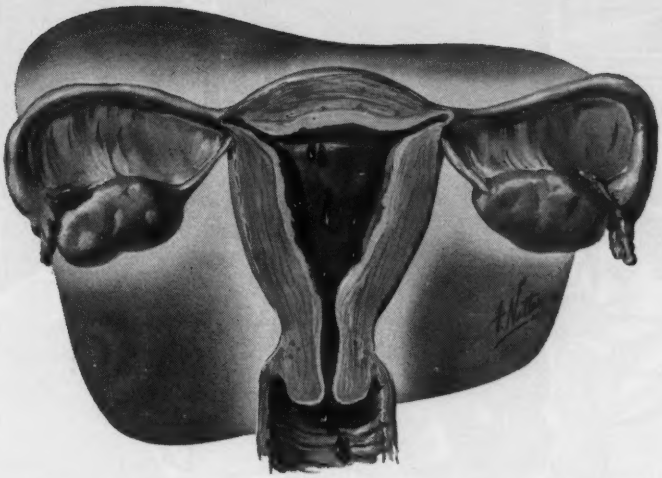

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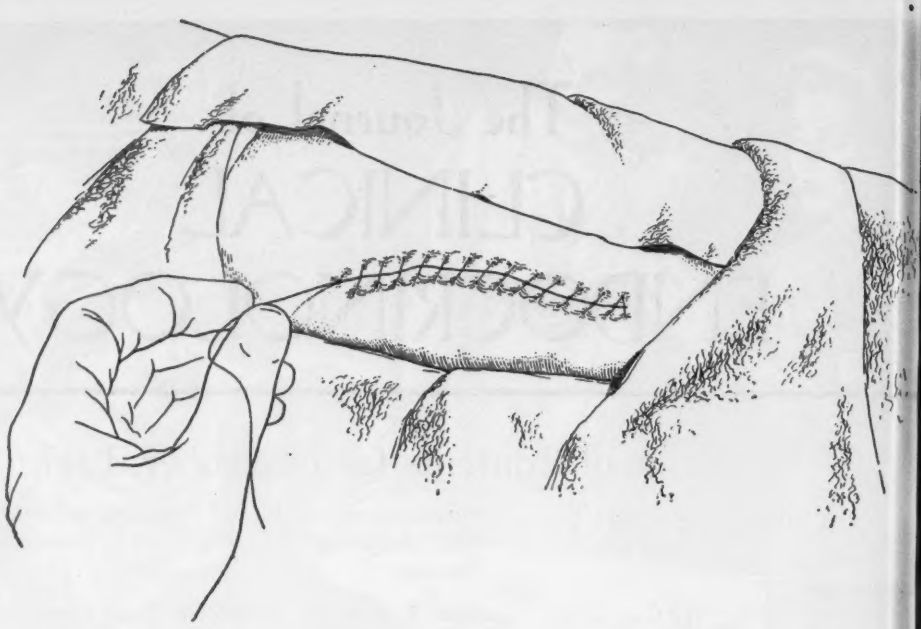

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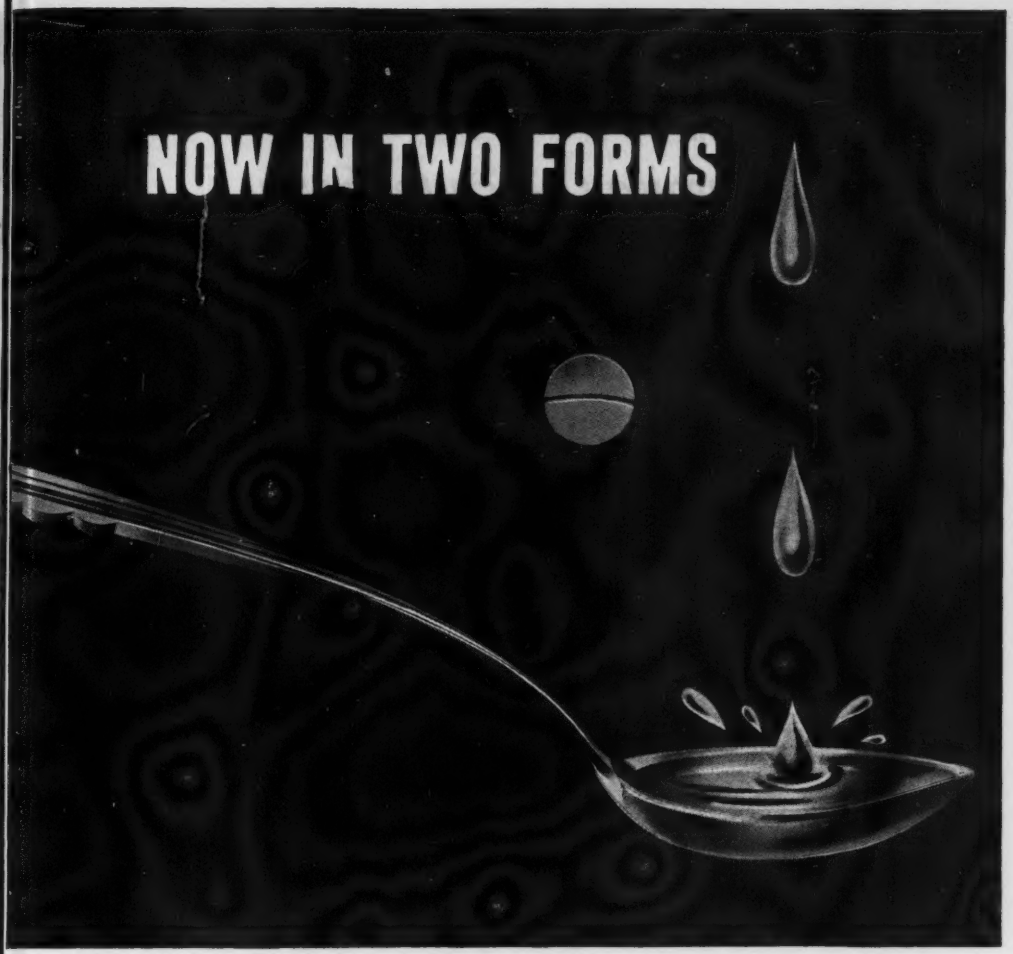

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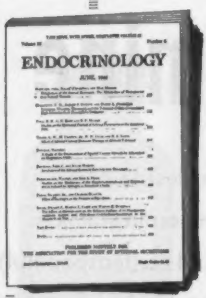

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